Project title: "A Phase II Therapeutic Trial of the Use of Dabrafenib and Trametinib in Patients with BRAF V600E Mutation Positive Lesions in Erdheim Chester Disease".

Draft/version number: 03-June-2014 / Version 1
Draft/version number: 16-July-2014/ Version 2
Draft/version number: 05-September-2014/Version 3
Draft/version number: 07-November-2014/Version 4; Amendment #1-A
Draft/version number: 26-March-2015/Version 5; Amendment #2-B
Draft/version number: 14-December-2015/Version 6; Amendment #3-C
Draft/version number: 26-January-2016/Version 7; Amendment #4-D
Draft/version number: 22-August-2016/Version 8; Amendment #5-E
Draft/version number: 17-Janaury-2017/Version 8; Update to Amendment #5-E
Draft/version number: 03-March-2017/Version 9; Amendment # 6-F (CTEP: Amendment #11)
Draft/version number: 16-June-2017/Version 10; Triennial Review
Draft/version number: 11-July-2017/Version 11; Problem 6 response and amendment.

NHGRI Protocol Number: 15-HG-0006

Principal Investigator: William A. Gahl, M.D. PhD

Title/Section/Branch/Institute: Clinical Director/Office of the Clinical Director/National Human Genome Research Institute.

IND/IDE reference number: CTEP Drugs

Collaborating Institutions: NCI; CTEP

Protocol Summary

Full Title:	"A Phase II Therapeutic Trial of the Use of Dabrafenib and Trametinib in Patients with BRAF V600E Mutation Positive Lesions in Erdheim Chester Disease".
Principal Investigator:	William A. Gahl, MD, PhD, Medical Genetics Branch, NHGRI
Sample Size:	N= 18
Accrual Ceiling:	18
Study Population:	Individuals with documented Erdheim-Chester Disease
Accrual Period:	January 2015 – January 2019
Study Design:	In this phase II open-label clinical trial, we clinically evaluate ECD patients with the BRAFV600E mutation and administer combination therapy with dabrafenib, a BRAFV600E inhibitor, and trametinib, an inhibitor of MEK, downstream of BRAF. We will determine the safety, tolerability, and efficacy of dabrafenib and trametinib in patients with ECD who harbor the BRAFV600E mutation. Patients are seen at 1 week, 1 month, 2 months, 4 months, and 6 months, 8 months, 10 months and 12 months to complete one year of therapy and off therapy follow ups will happen at 15 months, 18 months and 24 months to complete a 2-year trial. Target lesions will be assessed using RECIS criteria.
Study Duration:	Start Date: January 2015. End Date: January 2019.
Primary Objective:	To determine the safety, efficacy, and response rate of the combination of dabrafenib and trametinib in ECD.
Secondary Objectives:	Determine the time response, survival, and resistance to therapy.
Exploratory Objectives:	To monitor involvement and progression of disease and duration of treatment efficacy.
Endpoints:	The endpoint for an individual is reduction in target lesion size by RECIS criteria. For the trial, it is partial or complete response of at least 3 of the first 6 patients.

Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
CLIA	Clinical Laboratory Improvement Amendment of 1988
COI	Conflict of Interest
DHHS	Department of Health and Human Services
DSMB	Data Safety and Monitoring Board
GCP	Good Clinical Practice
ICF	Informed Consent Form
IRB	Institutional Review Board
N	Number (typically refers to number of subjects/sample size)
NHGRI	National Human Genome Research Institute, NIH
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSRP	Office of Human Subjects Research Program
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UP	Unanticipated Problem
WES	Whole Exome Sequencing
WGS	Whole Genome Sequencing

1.0 Precis

Erdheim-Chester Diseases (ECD) is a very rare non-Langerhans cell histiocytosis of unknown origin and pathogenesis. It has been reported mainly in adult males over the age of 40 years, although cases have been reported in females as well. Children are rarely affected. Mutation of the BRAF gene, specifically BRAFV600E, has been recently identified in 50% of Erdheim Chester lesions in a French cohort. This somatic mutation is believed to be the driver mutation in positive cases. Other genes that are involved in this disease process include NRAS, MAP2K1, PIK3CA, ARAF and other genes of the RAS pathway that are currently being studied. The clinical characteristics of ECD range from asymptomatic to multisystemic involvement; longitudinal progression and natural history are becoming better understood. ECD commonly affects the bones, kidneys, retroperitoneal space, skin and brain. If untreated, the disease progresses rapidly, causing fatal outcomes due to severe lung disease, chronic renal failure, cardiomyopathy and other complications. The diagnosis of ECD relies upon imaging studies and specific pathologic findings in biopsies of affected organs, i.e., fibrosis and infiltration of tissues with foamy histiocytes, lymphocytes, and plasma cells. Immunohistochemistry reveals cells positive for CD68 and CD163 and negative for CD1a, with 20% positivity to S-100. There is no standard treatment for ECD, although chemotherapy, radiation, stem cell transplantation, alpha-interferon, anakinra, imatinib and sirolimus have been proposed. The recent discovery of the BRAFV600E mutation in several ECD patients has opened a new area for treatment options. Vemurafenib, an FDA approved BRAF inhibitor for the treatment of patients with metastatic or unresectable melanoma with the V600E mutation, binds to this form of mutated BRAF causing protein inactivation. The use of vemurafenib in patients with ECD has been reported in 3 patients who experienced remission of the disease, and is currently being studied in the U.S. and Europe as monotherapy. Tumor/disease resistance to vemurafenib has occurred in melanoma and other cancers, although it has not been reported in patients with ECD. In this protocol, we propose to clinically evaluate ECD patients with the BRAFV600E mutation and administer combination therapy with dabrafenib, a BRAFV600E inhibitor, and trametinib, an inhibitor of MEK, downstream of BRAF. Screening for possible contraindications will be made prior to the administration of the first dose. With this trial, we will determine the safety, tolerability, and efficacy of dabrafenib and trametinib in patients with ECD who harbor the BRAFV600E mutation. Dabrafenib (which initial dose was 150mg BID, but due to high frequency pyrexia the dose was changed to 100mg BID for patients enrolled after amendment #6 of 12/27/2015) at a dose of 100mg will be given twice daily p.o.; trametinib 2mg will be given once daily p.o. Patients will be seen at 1 week, 1 month, 2 months, 4 months, and 6 months, 8 months, 10 months and 12 months to complete one year of therapy and off therapy follow ups will occur at 15 months, 18 months and 24 months to complete a 2 year trial.

2.0 Objectives and specific aims

2.1 Primary Objectives

2.1.1 - To study the efficacy and safety of dabrafenib and trametinib as combination therapy in patients with BRAFV600E positive Erdheim Chester Disease.

2.1.2 - To determine the clinical response rate to dabrafenib and trametinib combination therapy in patients with BRAFV600E positive Erdheim Chester Disease.

2.2 Secondary Objectives

2.2.1 - To determine time response, progression free survival and overall survival.

2.2.2 - To assess disease resistance to this combination therapy.

2.3 Exploratory Objectives:

2.3.1 - To monitor the degree of histiocytic infiltration-fibrosis progression, stability and regression under combination therapy using FDG-PET scan, MRI scans, CT scans and T-99m bone scans.

2.3.2 - To monitor serum CRP, ESR, and cytokine levels as inflammatory markers prior to and during combination therapy.

2.3.3 - To monitor renal function prior to and during combination therapy in order to assess for functional improvement.

2.3.4 - To evaluate the level of functioning, fatigue, motor skills and ability to perform routine daily activities prior to and during therapy in order to assess for improvements in these areas as well as quality of life improvement.

2.3.5 - To establish duration of treatment-endpoints in patients with BRAF V600E positive ECD lesions.

3.0 Brief rationale and background

3.1 Study Diseases:

The histiocytoses are a unique group of disorders with varied clinical presentations and outcomes. These disorders generally present in childhood; a recently increased frequency in adults reflects more accurate diagnosis in that age group. The histiocytoses cannot be categorized as entirely genetic, neoplastic, or reactive, and the pathophysiology remains poorly understood. For histiocytoses such as Langerhans cell histiocytosis and familial hemophagocytic lymphohistiocytosis, certain genetic associations have been made[27]. In addition, clonality has been proven for Langerhans cell histiocytosis, but not for other types of histiocytosis such as Rosai Dorfman disease, which involves the lymph nodes and sinuses. Because of the rarity of histiocytoses, clinical and basic research dedicated to these disorders has been insufficient. The histiocytoses have been divided into Langerhans cell

or non-Langerhans cell subtypes, with dendritic, macrophage/monocytic, and malignant forms[27].

The clinical presentation, progression, response to therapy and outcome varies in each of the different histiocytoses[12,18,23,27]. Patients can present with no symptoms, in which case the disease is diagnosed incidentally based upon involvement of a single organ system, or they can present with multisystem disease causing organ failure. Some patients with Rosai-Dorfman and juvenile xanthogranuloma may have a benign course or even exhibit regression without symptoms, while other patients progress to a complex multiorgan disease. Those histiocytoses classified as malignant generally prove fatal without treatment, and may progress even with treatment[27].

Erdheim Chester disease (ECD), first described in 1930[12], is a type of non-Langerhans cell histiocytosis that can present with no symptoms or only bone pain and fatigue, but can also present with multisystem involvement causing one or more of the following: cerebellar syndrome, panhypopituitarism, lung and cardiac disease, renal failure, bone disease and retroperitoneal fibrosis[18,29,38]. ECD is not considered a cancer, although recent findings of BRAF gene mutations suggest that ECD might represent a low-grade malignancy[19]. Its etiology and pathogenesis remain areas under active investigation. Animal models, cell lines and affected families are limited due to the rarity and sporadic nature of the cases. In fact, there have never been two patients in the same family with ECD.

ECD has been reported mainly in adult males over the age of 40 years, although females can be affected as well. Children are rarely affected. The pathophysiology of ECD has not been determined, but the disease results in part from an increased inflammatory response and intense immune activation. The principal players include interferon alpha, interleukin 1/interleukin 1 receptor antagonist, interleukin 6, interleukin 12 and monocyte chemotactic protein 1, indicating a Th-1 oriented systemic immune disturbance[3,18]. A mutation in the BRAF gene, BRAFV600E, has been recently identified in 50% of ECD lesions in a French cohort, with verification in U.S. patients[19]. Other genes that are involved in this disease process include NRAS, MAP2K1, PIK3CA, ARAF and other genes of the RAS pathway that are currently being studied. This somatic mutation may be responsible for the histiocytic infiltrations seen in ECD. The clinical characteristics of ECD range from asymptomatic to multi-systemic involvement. After diagnosis, ECD progresses rapidly, causing fatal outcomes due to severe lung disease, chronic renal failure, cardiomyopathy and other complications if left untreated. The diagnosis of ECD relies upon imaging studies and specific pathologic findings in biopsies of affected organs, i.e., fibrosis and infiltration of the affected tissues with foamy histiocytes, lymphocytes, and plasma cells. Immunohistochemistry reveals cells positive for CD68/CD163 and negative for CD1a; there is 20% positivity for S-100[17,18,27].

The natural history of ECD is still under investigation. Past literature describes the disorder as a condition that mainly affects males. The average age at diagnosis is 53 years and death from the disease occurs approximately 3 years after diagnosis. The typical presentation involves lower extremity bone pain, polyuria, polydipsia, fatigue and other nonspecific findings. Clinical evaluations reveal renal failure and inflammation with elevated CRP. Imaging studies show osteosclerosis, a "hairy" appearance to the kidney, and coated aorta on CT scan of the abdomen. Pituitary imaging usually shows a thickened pituitary stalk associated with signs and symptoms of diabetes insipidus and other hormonal disturbances. The differential diagnosis includes Paget's disease of the bone, lymphoma, pituitary adenoma, and granulomatous disorders. ECD can also be confused with adult onset storage disorders such as Gaucher disease and Fabry disease[12]. Pathology can be inconclusive; patients often remain undiagnosed and are treated empirically with steroids or chemotherapy.

In the past decade, the natural history of ECD has become better understood, with more than 400 cases reported since 1930. The first sign of ECD varies widely, since patients can present with many manifestations or be diagnosed incidentally. Increased awareness and research has increased the number of reported cases and shortened the time between presentation and diagnoses from up to 10 years to months or weeks, depending upon the medical institution involved. The frequency of the main manifestations varies from patient to patient. In our experience at the NIH with 32 patients, bone involvement, diabetes insipidus, retroperitoneal fibrosis and CNS disease are among the most common manifestations. Age at diagnosis ranges between 19 and 68 years. The average age of disease onset or first signs and symptoms is in the early thirties.

Diagnostic criteria for ECD have not been established, but the association of the pathological findings with elevated CRP, retroperitoneal fibrosis, pituitary stalk involvement and T-99m bone scan showing increased radiotracer uptake in the long bones are highly suggestive of ECD[18]. Pathology along with a positive bone scan can establish the diagnosis.

There is no standard treatment for ECD. Since the exact etiology is not known, there are no approved drugs for this condition. Patients have been treated empirically with interferon alpha (3-9 million units; 135mcgr pegylated form) weekly or high dose (>18 million units; >180mcgr pegylated form), anakinra (100mg SC daily), imatinib (400mg daily), steroids, and chemotherapy such as cladribine given in 6 cycles. Less frequently used drugs include rapamycin, tocilizumab and infliximab. No clinical trials have been performed to assess the safety and efficacy of these medications; their use is anecdotal, patient therapy is modified on an individual basis, and the results are not promising. Patients with CNS disease are the group with the worst morbidity and mortality.

ECD Treatments

Interferon alfa: Hervier et al[23]. studied the efficacy of high dose (≥18 million units or ≥185mcgr PEG) vs standard dose (9 million units or 135mcgr PEG) interferon alpha in 24 patients with ECD and stability or improvement was seen in 67% of patients. The severity of the disease was key in patient response to interferon therapy; CNS and heart disease are the most difficult to treat and require high-dose interferon. Remission was partial and recovery was never seen. Prolonged treatment is suggested, up to several years. Treatment may not be tolerated by all patients due to side effects.

Table 1. Results of Interferon Alpha Treatment for ECD

Interferon regimen	Stability	Improvement	Worsening	No data
Low dose : 9M units or 135mcgr PEG	6/24	1/24	5/24	12/24
High dose: ≥18M units or ≥185mcgr PEG	7/24	11/24	6/24	0/24

Imatinib: Janku et al[28] reported the use of imatinib in 3 patients with histiocytosis. Response was seen within weeks of therapy, but the mechanism of action that elicited this response was not determined. The response might be explained by the inhibition of platelet derived growth factor receptor beta (PDGFB), which can be expressed in LCH and ECD histiocytoses and that inhibits the differentiation of CD34 positive cells to dendritic cells. Patients either had disease stability or progression after months of therapy. Recovery was not seen and prolonged treatment is recommended.

Anakinra: Aouba et al[3]. promoted the use of anakinra as salvage therapy in ECD. They treated 3 patients with ECD localized mainly to bone and the retroperitoneal space; resolution of symptoms was seen in all patients as well as decrease of the retroperitoneal fibrosis in two patients. The anakinra dosage was 100mg subcutaneous once a week and treatment was prolonged. Anakinra has not been used in severe ECD affecting organs such as lungs, heart, cerebellum, brain and pituitary. No specific duration of treatment was recommended.

Tran et al.[42] treated a 10 year old girl diagnosed with ECD after presenting with elevated CRP and ESR as well as bone pain and failure to thrive. Imaging showed bone marrow and retroperitoneal involvement. The patient was initially treated with IFN 2a 3M units 3 times a week; this resulted in improvement after 4 months. After 10 months of treatment, the

patient presented with fever, bone pain and increased ESR and CRP. Treatment with IFN was stopped and vinblastine and prednisone were given instead. This therapy showed no efficacy and PEG IFN 2a was started with good efficacy, but relapse was reported 12 months later. Anakinra was then started at 2mg/kg/day and within one week, fever and bone pain resolved. ESR and CRP were normal after one month. After 7 months of therapy, the patient remained stable, but bone marrow and retroperitoneal disease was unchanged.

Anakinra also lacks efficacy in treating CNS disease.

Cladribine: Adam et al.[1,2] reported the use of cladribine as a highly effective medication in patients with extensive disease including the CNS. Cladribine has very good tolerance as monotherapy, and is an effective drug for diseases of the juvenile xanthogranuloma group (ECD, diffuse juvenile xanthogranuloma and Rosai-Dorfman disease). In total, 7 publications describe a therapeutic response to cladribine in ECD, disseminated juvenile xanthogranuloma and a localized form of plane xanthoma type. Some patients experienced a total response; there was remission in most of the cases. In one case follow up was for16 months.

In our experience at the NIH CC, we have seen 4 patients treated with cladribine. One had no response and is currently stable with imatinib. The other 3 patients had response with no progression of disease and recovery demonstrated by improvement of quality of life and energy. ECD lesions decreased in size, but there remains evidence of disease on imaging.

Other treatments include anecdotal use of steroids, rapamycin, tocilizumab and infliximab, but data are lacking. Currently rapamycin, tocilizumab and infliximab are being studied in Italy.

In this protocol, we propose to clinically evaluate ECD patients with BRAFV600E and assess the efficacy of treatment with the BRAF/MEK inhibitors dabrafenib and trametinib as combination therapy. Screening for possible contraindications will be performed prior to the administration of the first dose.

Even though all these treatments have been used and results can be promising in a number of cases, the authors and treating physicians recommend that larger series and formal clinical trials be developed to assess the true efficacy of these or other therapies. Although treatment duration has not been determined, patients continue to be treated for years with medications such as interferon, anakinra and imatinib.

Recently, the BRAFV600E mutation was identified in 50% of ECD patients (N=24) in France, and cases are being reported in the U.S. Three ECD patients treated with vemurafenib showed disease regression. Specifically, Haroche et al[18] treated 3 ECD patients with BRAF V600E positive lesions with 1920mg of vemurafenib twice daily. The dose had to be decreased to 960mg twice daily in all patients due to cutaneous lesions. All

patients had improvement within weeks, as demonstrated by a decrease in CRP, CT and FDG PET scan evidence of decrease in size of lesions, and decreased FDG uptake on PET Scans. This was a small series, but other patients are being seen and followed in the U.S. and Europe; see summary below.

Table 2. Results of Vemurafenib Treatment in 3 ECD Patients[20]

Patient	Initial Treatment	Vemurafenib*
Patient 1 65 year old male with ECD affecting bones and retroperitoneal space causing hydronephrosis. Thick pericardium and elevated CRP and LFTs.	6/2011- 135mcgr PEG IFN for 4 weeks than increased to 180mcgr. Chemistry and imaging studies were unchanged or worsened. Dose adjusted to 180mcgr-270mcg alt days. Treatment stopped on 3/2012 due to inadequate response, depression and side effects.	4/2012 – Vemurafenib started. CRP, GGT, PET scan, CT and skin lesions showed improvement by day 30.
Patient 2 59 year old female with ECD affecting skin, pituitary, retroorbital space, heart, retrosternal space and bones.	3/2011 – 135 mcgr PEG IFN started with partial response, eye pain and heart disease remained. Dose increased to 180mcgr on 6/2011. Stopped on 3/2012 due to depression, fatigue, neutropenia, and inefficacy in retroorbital disease.	4/2012 – Vemurafenib started. Symptoms disappeared and CRP improved by day 30. Repeat skin biopsy showed no histiocytes; PET scan and CT improved.
Patient 3 31 year old female with ECD affecting skin, heart, retroperitoneal space, bones and pituitary.	4/2010 – 135mcgr PEG started. On 2/2012 deterioration seen with increased pain and xanthelasma. 3/2012 IFN dose increased to 180mcgr with no effect.	5/2012 – 30 days later improvement seen with decrease in CRP and skin lesions. PET scan showed decreased uptake and heart disease improved.

* All patient were initially treated with 1920mg/d BID, dose was tapered to 960mg/d in all patients due to skin side effects. Follow up time was short and current status is unknown for us.

In the U.S., at least 4 other patients are being studied under a therapeutic trial for BRAF V600-mutated cancers, but results are not yet available and the patients are being compared with patients having other active malignancies. To our knowledge, a total of 6 ECD patients have been treated with vemurafenib, and two of them withdrew from the trial due to side effects.

Toxicities related to BRAF inhibitor therapy require coordinated multidisciplinary management. In clinical trials of vemurafenib, the most common side effects reported were arthralgias, rash, fatigue, nausea, and alopecia. Additionally, cutaneous squamous cell carcinomas (SCCs) or keratoacanthomas have been reported in approximately 20% of patients treated with vemurafenib. Dabrafenib has been associated with hyperkeratosis, cutaneous SCCs, keratoacanthomas, and pyrexia[15,21,40].

Based on the melanoma and other malignancy experience, the majority of patients with a BRAF mutation should benefit from BRAF inhibitor therapy. However, approximately 10% of cancer patients with a BRAFV600E mutation have tumor progression early in the course of therapy. Furthermore, despite seeing an initial clinical response, the vast majority of patients have residual tumor following maximal response and most ultimately relapse in less than a year. In melanoma patients, resistance to vemurafenib has developed after 6 months of treatment in some individuals. This can also be seen with dabrafenib if used alone.

Gaining further insight is critical to the development of rational strategies to effectively overcome this resistance. Reactivation of MAPK , downstream of BRAF, was proposed as a primary mechanism of resistance, but alternative pathways also play a critical role. In contrast to oncogene targeted therapies that have been used with success in other malignancies, resistance to BRAF inhibition does not appear to be due to the accumulation of mutations in BRAF itself, with decreased drug binding[37]. Rather, a number of preclinical studies have shown that persistent activation of the MAPK pathway through oncogenic NRAS may be one mechanism of acquired resistance. This would result in sustained hyperactivation of MEK and ERK.

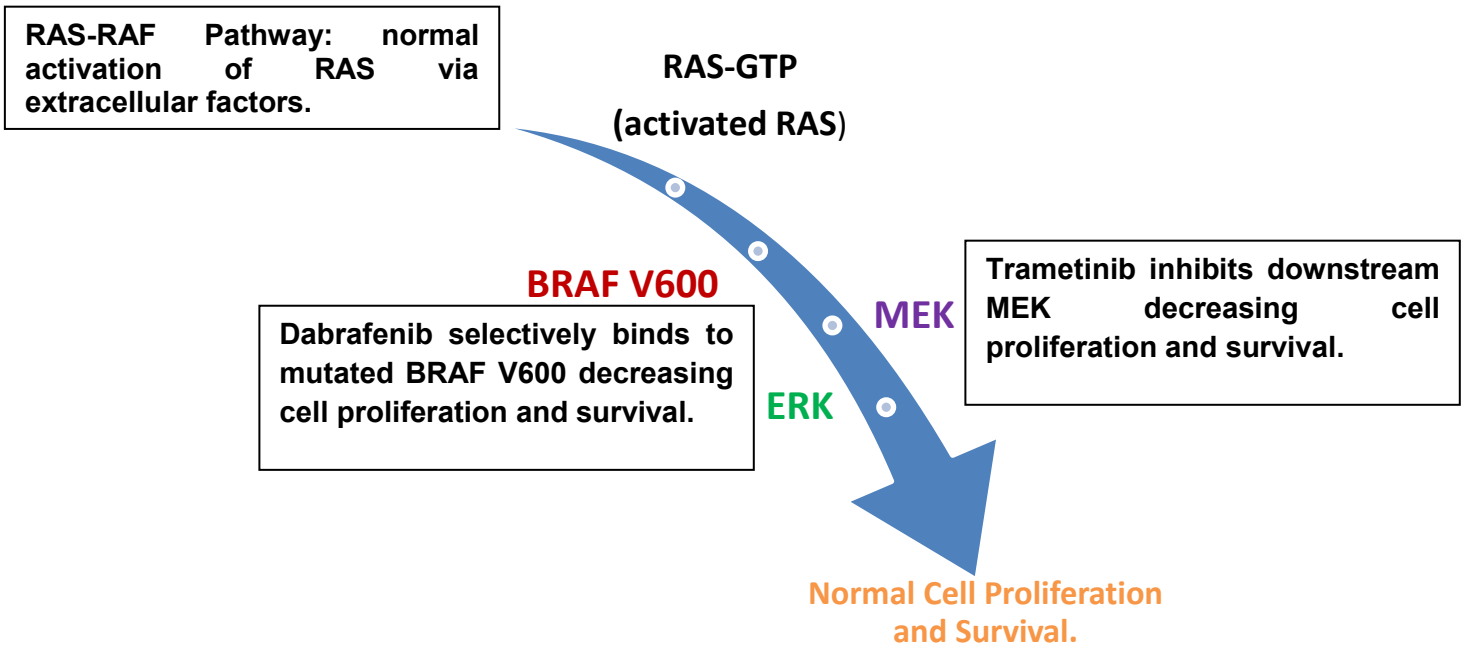
To prevent resistance to BRAF inhibitors, the MEK inhibitor trametinib will be used in combination as a downstream inhibitor for superior therapy and prevention of resistance. The use of this therapy should inhibit histiocytic proliferation and fibrosis, decrease the degree of inflammation, reduce lesion size, improve the level of activity and physical functioning of the patients, and increase their energy level. Dabrafenib at 150mg BID with trametinib at 2mg once daily was the original dose regimen for this trial, but due to the high frequency of pyrexia the dose of dabrafenib was changed to 100mg BID for patients enrolled after amendment #6 of 12/27/2015; trametinib 2mg once a day remains at the same dosage as for the original regimen.

The episodes of pyrexia were frequent among the currently enrolled patients, with patients having more than 5 episodes of pyrexia regardless of optimal steroid use and interruption of therapy. After the dose of dabrafenib was modified to 100mg twice daily or 75mg twice daily, the episodes of pyrexia decreased or did not recur; this is the reason why the initial dose of dabrafenib was modified.

3.2 Rationale:

BRAF, also referred to as proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B1, is a protein kinase within the RAS-RAF signaling pathway. This pathway regulates the expression of genes that control many cellular functions such as cell proliferation, cell survival, cell differentiation and apoptosis. Mutations in the BRAF gene result in activation of the BRAF protein. More than 30 mutations of the BRAF gene have

been associated with human cancers, including papillary thyroid cancer, melanoma, colon and ovarian cancer. BRAF mutations are also associated with other genetic disorders such as Noonan syndrome, Leopard syndrome and cardiofasciocutaneous syndrome, but these are inherited disorders, not due to a somatic mutation as for ECD. Mutated BRAF may promote overactive signaling and cell proliferation. Hence, dabrafenib, which selectively binds to the $BRAF^{V600E}$ mutated gene producing protein inactivation, and trametinib, a MEK inhibitor, combine to achieve downstream inhibition of the pathway, potentially leading to apoptosis of the mutant cells.



Despite many and varied attempts with known therapies, patients with ECD succumb to the disease within a few years of diagnosis. Several specific complications are associated with patient deterioration and death. Cord compression causing paralysis increases the risk of infection and sepsis due to the bedridden condition of patients. Renal failure causes toxic shock, and pulmonary fibrosis causes respiratory failure and right heart failure. For this reason, combination therapy with dabrafenib and trametinib should be studied in the subset of ECD patients that can potentially benefit based upon their molecular pathology status.

4.0 Description of study design

This will be a phase II trial with no randomization. For complete description of the study design and statistical considerations, please see sections 5.6.1 and 9 which discuss the description of study statistical considerations and/or analytic plan.

5.0 Description of procedures:

5.1 Diagnostic tests and procedures

Certain laboratory and imaging studies will have been performed as part of the natural history protocol for ECD. However, the studies described in this Section will be performed specifically for this treatment protocol. Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. See study calendar below.

Table 4. Study Calendar

	Pre-Study	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 16**	**Wk 24**	**Wk 32**	**Wk 40**	**Wk 48**	**Off Therapy Wk 60**	**Off Therapy Wk 72**	**Off Therapy Wk 96**
Dabrafenib mesylate (GSK2118436B) (NSC 763760)		A	A	A	A	A	A	A	A	C	C	C
Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093)		B	B	B	B	B	B	B	B	D	D	D
Informed consent	X									Reviewed and re-consented as needed.	X	X
Demographics	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent meds	X	Througout the study and modified as needed.										
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X
Weight and Nutrition	X	X	X	X	X	X	X	X	X	X	X	X
Performance, RPM,	X	X	X	X	X	X	X	X	X	X	X	X

Cardiology	X		X	X	X	X	X	X	X	As needed per clinical assessment	X	X
Dermatology	X		X	X	X	X	X	X	X	X	X	X
Ophthalmology	X		X	X	X	X	X	X	X	X	X	X
Neurology	X		X	X	X	X	X	X	X	X	X	X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X
24h Urine[a]	X		X	X	X	X	X	X	X	Instead of 24 urine collections, random testing will be performed instead.	X	X
Serum chemistry[b]	X	X	X	X	X	X	X	X	X	X	X	X
Blood hematology[c]	X	X	X	X	X	X	X	X	X	X	X	X
PBMC Cytokines	X			X		X			X		X	X
EKG	X		X	X	X	X	X	X	X	X	X	X
Echocardiogram	X		X	X	X	X	X	X	X	X	X	X
MUGA	As needed											
Adverse event evaluation	Throughout the study											
RECIST 1.1 Tumor Size (MRI and CT)[E]	X		X	X	X	X	X	X	X	Only target lesions will be monitored at 60-72-96 wks f/u minimizing scans and radiation.	X	X
FDG-PET	X			X	X	X	X	X	X	X	X	X
Bone scan	X			X	X	X	X	X	X	X	X	X
B-HCG	X[d]		X	X	X	X	X	X	X	X	X	X

*Other tests, as appropriate**	X			X	X			X		X	X	X
Other correlative studies (Proteomics) [f]	X[f]	When possible										

A: Dose as assigned; *administration schedule for 48 weeks (12 cycles). Therapy will stop after 12 cycles and patient will be followed for 48 weeks off therapy*

B: Dose as assigned*; administration schedule for 48 weeks (12 cycles). Therapy will stop after 12 cycles and patient will be followed for 48 weeks off therapy*

C-D: Off therapy, *if PD is seen during follow up and prior to 96 weeks off therapy, therapy will be resumed at the dose level of the last cycle. Patient needs to meet all eligibility criteria once more before therapy is resumed. Duration of therapy will be discussed with the CTEP monitor.*

E: During the off therapy follow up period, MRI and CT scans will performed based on the target lesions followed on each case. All patient will have a whole body PET-CT and bone scan performed.

a: Volume, creatinine, protein, glucose, phosphate, BRAF V600E DNA assay

b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium, GGT, cholesterol, triglycerides, HDL, LDL, uric acid

c: ESR, CPR, PT, PTT

d: Serum pregnancy test (women of childbearing potential); must be performed within 14 days of the first dose of study treatment.

e: Off-study evaluation.

f: Proteomics will be performed on biopsies of accessible tumor tissue, when available.

g: Dermatology evaluations will continue for 6 months after the last dose of the study agents.

* For some patients, testing will be customized based upon clinical manifestations. In those cases, certain of the following studies will be performed at baseline and at 2, 6 and 12 months; EMG, EEG, PFTs, NO and other clinical indicated tests.

\+ After problem No. 6 (June 21, 2017), BRAF V600E quantification through blood and urine was removed from the study. This also applies to the Spirituality tool administered through PPC.

5.1.1 - Laboratory tests.

At the initial NIH Clinical Center admission for this protocol, a baseline history and physical examination and several laboratory tests, procedures, and consultations will be performed on all patients. After all screenings are completed, each patient's information will be recorded and disease severity will be analyzed. Patients will remain on any supplements and non-ECD medications that they have been receiving, except for prohibited drugs, e.g., those listed in Section 4.3. After the start of therapy, admissions to the NIH CC will occur at 1 week, one month, 2 months, 4 months, 6 months, 8 months, 10

months and 12 months. After the completion of 12 months of therapy, patients will be followed at 15 months, 18 months and 24 months in order to allow for monitoring of disease stability and recurrence off therapy. Patients can also be seen and evaluated at outpatient clinics or day hospitals during follow up visits.

Testing will be individualized based upon clinical findings, but certain studies will be performed on every patient.

Laboratory tests will include one 24-hour urine collection for determination of renal tubular and glomerular function. The urine will be measured for volume and assayed for creatinine, protein, glucose, and phosphorus; a simultaneous serum creatinine will permit determination of creatinine clearance. A urinalysis will be performed. Blood will be drawn for CBC and differential, platelets, erythrocyte sedimentation rate, C-reactive protein, and an SMA-14 panel including electrolytes, calcium, magnesium, phosphorus, liver enzymes, gamma glutamyltranspeptidase, alkaline phosphatase, bilirubin, creatine phosphokinase and uric acid and glucose. Cholesterol, triglycerides, HDL, LDL prothrombin time and partial thromboplastin time will also be obtained. Serum pregnancy test will be performed on all females at every visit prior to imaging procedures. Also, serum pregnancy test must be performed within 14 days of the first dose of study treatment. The amount of blood required for these tests will be ~30 mL. In addition, PBMC cytokine analysis requires ~40 mL of blood. These volumes are consistent with NIH guidelines, and the blood will be collected in two separate draws. No more than 10.5 mL/kg or 550 mL, whichever is smaller, will be drawn for research purposes over any 8-week period, and no more than 5 ml/kg will be drawn in any single day. We expect that all of our study participants will undergo these blood tests as part of their participation.

If possible, biopsies of accessible tissue (e.g., bone, kidney, skin) will be obtained at baseline and at subsequent admissions to assess for changes in tissue proteomics associated with therapy.

In addition, if blood drawing limits permit, up to 30 ml of blood may be removed for research purposes, such as to analyze for metabolites that may be recognized in the future as markers of disease. These will be attempted while patients are on therapy

5.1.2 Procedures and Imaging.

Certain procedures and imaging will be performed as part of the ECD natural history protocol. For this treatment trial, however, a specific set of studies will be performed to follow the lesions whose sizes serve as outcome measures. The baseline measurements must be performed at the initial baseline admission or within 4 weeks prior to baseline. The studies are:

- Chest /abdomen and pelvis CT with contrast, for abdominal and lung involvement.

- Brain/cerebellar/orbital/pituitary MRI with gadolinium (unless EGFR is <30).
- Cardiac CT with contrast and cardiac MRI. These imaging studies will be performed through NHLBI protocols 12-H-0141 ("Prospective Evaluation of New Techniques in Radiation Reduction for Cardiovascular Computed Tomographic Angiography") for cardiac CT and 02-H-0050 ("Technical Development of Cardiovascular Magnetic Resonance Imaging") for cardiac MRI.

- Echocardiogram and electrocardiogram will be performed on every visit except the one week follow up.

These outcome measures will be assessed using RECIST criteria at every scheduled admission except the 1 week visit.

In addition, the following studies will be performed on all patients, but will serve as exploratory outcome measures, since RECIST criteria are not adequate:

Performed at baseline, 1, 2, 4, 6, 8, 10 and 12 months:

- Pulmonary function tests, echocardiogram, and electrocardiogram to evaluate cardiopulmonary function

Performed at baseline, 2, 4, 6, 8, 10 and 12 months:

- Whole body technetium 99-MDP bone scan to assess bone involvement.
- Whole body 18-FDG PET scan including brain to evaluate for visceral involvement.

Studies performed at 15, 18 and 24 months (off therapy) follow up visits will include:

- Chest, cardiac, abdomen or pelvic CT with contrast depending on the location of the target lesion followed on each case.
- Brain, cerebellar, pituitary or orbital MRI with gadolinium depending on the location of the target lesion followed on each case.
- Whole body technetium 99-MDP bone scan to assess bone involvement and whole body 18-FDG PET scan including brain to evaluate for visceral involvement. These 2 modalities will help in determining disease recurrence according to the degree of uptake of the T-99MDP and FDG.
- Pulmonary function tests, 6 minute walk, echocardiogram, and electrocardiogram to evaluate cardiopulmonary function

Consultations for all patients in this treatment trial will include an ophthalmology examination to evaluate orbital and optic nerve involvement as well as possible side effects of the trial therapy. All patients will be evaluated by neurology and dermatology, to assess the extent of disease and to evaluate response and side effects during therapy. All patients will also see the Rehabilitation Medicine service for a 2-hour assessment, with evaluations by physical therapy, occupational therapy and, if indicated, speech and language pathology.

Rehabilitation Medicine will complete the MD Anderson Symptom Inventory Core Items form. For an additional assessment of function, patients will be evaluated using the multi-dimensional fatigue inventory, 6-minute walk test, Craig hospital inventory of environmental factors, human activity profile, NINDS-Neuro-QOL scale, activity card sort, comparative pain scale, single leg stance, functional reach and grip strength using a dynamometer, and the group peg board test for fine motor dexterity. Quality of Life measures will include the Activity Card Sort and an NINDS measure.

Clinical evaluations will also be performed during the off therapy follow up period. Please refer to section 4.1 Table 4: Study Calendar, for further details on these evaluations during the off therapy follow up period.

5.1.3 Correlative Studies Background.

The mechanisms by which BRAF mutations result in ECD remains unknown, but might involve intracellular signaling pathways (e.g., MEK) or unregulated inflammation. Proteomic studies of histiocytic ECD tissues, with emphasis on intracellular signaling proteins, can address the first possibility; accessible tissue (e.g., bone, kidney, skin) will be obtained at baseline when possible and also at subsequent follow-up admissions, when possible and while patients are on therapy. PBMC cytokine analysis, along with ESR and CRP measurements, can address the second possible mechanism. These studies will be performed at baseline and at the 2, 6, 12, 18 and 24 month return admissions or outpatient visits; these studies are further described in Section 5.1.6

5.1.4 Biomarker, Correlative, and Special Studies.

5.1.4.1 Biomarker Studies

Biomarker: Tissue BRAF Mutation Analysis (**INTEGRAL**)

Erdheim Chester disease has been associated with BRAF V600E mutation in at least 50% of patients affected by this condition. Current therapy is empirical and even though clinical stability is achieved in many cases, progression occurs and patients do not develop significant recovery. The association with the BRAF defect opens new doors for targeted treatment. The use of BRAF inhibitors has been reported in a small series (3 cases). Vemurafenib was the BRAF inhibitor used and patients experienced clinical improvement within 30 days of treatment. Continued follow up of these patients has not been reported, but the treating physicians emphasized the need for formal clinical trials to assess the efficacy of BRAF inhibitors. They also made note of the possibility of resistance to BRAF inhibitors as seen in other conditions such as melanoma, prompting consideration of combination therapy. Molecular profiling of patients with ECD should be part of their diagnostic testing since targeted therapy is available for molecular findings associated with the BRAF gene. Impairment of the RAS pathway through the inhibition of BRAF and

MEK with the use of dabrafenib and trametinib should stop disease progression, reduce the size of ECD lesions, improve organ and system functions, decrease inflammation and fatigue, improve physical functions, and increase survival.

The BRAF gene will be sequenced for all patients enrolled in NHGRI clinical protocol 11-HG-0207, which performs clinical and basic investigations into Erdheim Chester disease. Subjects in whom the BRAF V600E mutation (gain of function mutation) is detected will be eligible for enrollment in this therapeutic trial; dabrafenib and trametinib will be used as BRAF pathway inhibitors. The BRAF V600E mutation will serve as an integral marker for inclusion criteria and treatment assignment.

Enrollees of the NHGRI study 11-HG-0207 will have BRAF testing performed in either of two CLIA-certified molecular pathology laboratories.

- Molecular pathology laboratory at NIH Clinical Center in Bethesda, MD under the supervision of Dr. Mark Raffeld.
    - MOLECULAR PATHOLOGY LABORATORY AT NIHCC

  CLIA: 21D0716664
  EXPIRATION: 7/16/2016

- Molecular pathology laboratory at Quest Diagnostics Nichols Institute in Chantilly, VA under the supervision of Dr Albert Ho MD PhD.
    - QUEST DIAGNOSTICS CHANTILLY, VA.

  CLIA: 49D0221801
  EXPIRATION: 2/8/2017

BRAF V600E mutation testing performed on patients locally will be repeated for verification in one of the above laboratories.

Description of assays:

- MOLECULAR PATHOLOGY AT NIH Clinical Center:

BRAF mutation analysis is performed through DNA extracted from paraffin-embedded tissue and sections prepared using the Qiagen QIAamp DNA FFPE Tissue Kit. The surgical pathology diagnosis is required prior to testing. The percentage of atypical cells is preferred to be >15%, a lower recommended limit for mutation detection.

In the first assay, the DNA is then subjected to COLD-PCR using a single primer set one encompassing codons 599-601 of the BRAF gene. The product is then subjected to pyrosequencing using a Qiagen PyroMark Q24 system. The BRAF mutation assay as implemented and validated in this laboratory has an analytic sensitivity of about 3% tumor cells (1.5% of alleles). However, given the variability of estimating the percentage of tumor cells in tissue, there is potential for false negative results in tissues that contain less than 10% tumor cells. Only the V600E and V600K mutations are detected with this assay.

The second assay is a sensitive allele specific assay that only detects V600E, (T>A). This assay has a sensitivity reaching 0.2% tumor cells or better. The lab has never had a false negative with this assay as defined by a case detected by pyrosequencing and missed by the allele specific PCR. However, there is no good way to measure false negatives when the tumor percentage falls below detection by the other methods.

- QUEST DIAGNOSTICS:

Quest's molecular oncology tests for the detection of BRAF mutations include:

- BRAF mutation analysis by DNA-based PCR – sequencing to detect somatic mutations on exon 11, 12, and 15 of BRAF

- BRAF mutation analysis using ultra-sensitive ASO (allele specific oligonucleotide) PCR methodology.

The assay is performed on FFPE blocks, or H & E with 6-8 unstained slides in 5 micron sections with >10-15% of tumor cells. If no mutations are present as described in the 16767 BRAF molecular reports by mutation type and/by the words "non-detected", the assay will automatically be reflexed to determine if the V600E gene is present by an ultra-sensitive ASO (allele specific oligonucleotide) PCR methodology. The interpretation will expand to include the following detail about the V600E gene: "This provides both optimal sensitivity for codon 600 mutations (V600E) and broader mutation detection of other activating BRAF mutations seen in melanoma as well as report information specific to the DNA based PCR sequences."

The sensitivity of BRAF AS-PCR is 0.1% V600E mutation bearing cells. It does not detect other mutations. The sensitivity of Sanger sequencing is 15-20% tumor cells in a background of non-neoplastic cells. It can detect other BRAF mutations.

5.1.5 -Pharmacokinetics Studies

N/A

5.1.6 - Laboratory Correlative Studies

Three biological studies will be performed for drug effects. First, PBMC cytokines will be assessed at baseline, 2 months, 6 months, 12 months after initiation of treatment and 18 and 24 months during the off therapy follow up period. These cytokines will include both pro- and anti-inflammatory molecules, i.e., IL-1, IL-2, IL-1ra, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, GM-CSF, IFN, IP-10, TNF, and they will be analyzed in the NIAMS laboratory of Dr. Massimo Gadina. We also plan to obtain plasma cytokine array data.

Second, tissue proteomics will be performed by the Proteomics Core Laboratory of MD Anderson. The proteomics platform interrogates a broad array of proteins, but our

investigations will specifically target components of the BRAF-MEK signaling pathway. These include BRAF, NRAS, KRAS (if available), MAPK, MEK, PI3K, mTOR, and ERK, AKT, and JAK2 if available. Tissue will not be available from every patient, but we will attempt to obtain biopsies of accessible tissue (e.g., bone, kidney, skin) at baseline for future comparisons. Post-treatment tissue will be obtained on return visits when biopsies are medically indicated or readily available.

5.1.7- Special Studies

We will obtain special stains for histological markers on histiocytic biopsy material, if funding permits.

5.2 Medical information

Medical summaries and laboratory test results will be collected and the information stored in a locked file cabinet and treated as confidential clinical data. Besides this, participant's information will be stored in a database under password such as Lab Matrix. Only the principal investigator, associated investigators and laboratory staff working with research samples will have access to this database.

5.3 Diagnostic studies

Diagnostic studies will be performed as stated in section 5.1.

5.4 Biological Specimens

Biological specimens will be addressed as stated in section 5.1.

5.5 Approved Drugs Being Used for Research

NCI Supplied Agent(s): Dabrafenib mesylate (GSK2118436B) (NSC 763760) and Trametinib dimethyl sulfoxide (GSK1120212B, MEKINIST™) (NSC 763093) have been approved for the treatment of unresectable and metastatic melanoma.

5.6 Unapproved Drugs/Devices

NCI Supplied Agent(s): Dabrafenib mesylate (GSK2118436B) (NSC 763760) and Trametinib dimethyl sulfoxide (GSK1120212B, MEKINIST™) (NSC 763093)

IND #: 119346

IND Sponsor: DCTD, NCI

5.6.1- CTEP IND Agent(s)

5.6.1.1- Dabrafenib Mesylate (GSK2118436B)[24]

The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers. This pathway can be constitutively activated by molecular alterations including BRAF activating mutations. Approximately 90% of all identified BRAF mutations in human cancer consist of a T1799 transversion mutation in exon 15, which results in a V600 E/D/K (T1799A) amino acid substitution. This mutation appears to mimic regulatory phosphorylation and increases BRAF activity approximately 10-fold compared to wild type (wt). RAF is a validated target in BRAF V^{600E}-containing melanoma. In August 2011, the FDA approved vemurafenib (PLX4032, Zelboraf®), an ATP-competitive selective RAF inhibitor for the treatment of late-stage $BRAF^{V600E}$ melanoma. In the pivotal phase III trial of vemurafenib *vs.* dacabazine (Chapman *et al.,* 2011), vemurafenib demonstrated significant improvement in overall survival (OS) (6-month OS of 84% *vs.* 64%, hazard ratio [HR]=0.37; $P<0.001$), progression-free survival (PFS) (estimated median PFS of 5.3 months *vs.* 1.6 months (HR=0.26; $P<0.001$]), and overall response rate (ORR) (48% *vs.* 5%). However, in patients with colorectal cancer (CRC) bearing the BRAF V600E mutation, there was only one partial response (PR) among 20 patients treated (ORR 5%) and four minor responses (Kopetz *et al.,* 2010).

Dabrafenib mesylate (GSK2118436B, Tafinlar®; referred to as dabrafenib hereafter), a 4-(3-aminosulfonylphenyl)-5-(pyrimidin-3-yl) thiazole, is an ATP-competitive, selective inhibitor of RAF kinase currently in clinical development. On May 29, 2013, the U.S. FDA approved dabrafenib for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by an FDA-approved test (FDA, 2013). On January 10, 2014, the FDA granted accelerated approval to dabrafenib and MEK inhibitor trametinib for use in combination to treat patients with unresectable or metastatic melanoma with either $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation as detected by an FDA-approved test (FDA, 2014).

5.6.1.1.1- Mechanisms of Action and Preclinical Data with Dabrafenib

Dabrafenib potently inhibits all RAF isoforms, with the strongest potency against the V600 mutant, as compared to its activity against wt BRAF and CRAF (see below). In a panel of more than 270 kinases tested outside RAF isoforms, only 10 kinases were inhibited at a 50% inhibitory concentration (IC_{50}) <100 nM: LIM domain kinase 1 (LIMK1), activin receptor-like kinase 5 (ALK5)/ transforming growth factor (TGF)-beta receptor type-1 (TGFβ1R), Never In Mitosis Gene A (NIMA)-related kinase 11 (NEK11), salt-inducible

kinase 1 (SIK1), salt-inducible kinase 2 (SIK2), polycystin-2 (PKD2), protein tyrosine kinase 6/breast tumor kinase (BRK), pancreatic eukaryotic initiation factor-2 alpha (eIF2α) kinase (PEK)/eIF2α kinase (PERK), endothelium-specific receptor tyrosine kinase 2 (TIE2) (R849W), and yeast casein kinase 1 (CK1) (IB, 2013a).

Table 5. Inhibitory Activity of Dabrafenib on BRAF

	$BRAF^{V600E}$	$BRAF^{V600K}$	$BRAF^{V600D}$	wt BRAF	CRAF
IC_{50}	0.65 nM	0.50 nM	1.84 nM	3.2 nM	5.0 nM

In a panel of >110 human tumor cell lines with confirmed BRAF mutational status, dabrafenib potently inhibited proliferation of a majority (73%) of $BRAF^{V600E}$ mutant cell lines with growth IC_{50} (gIC_{50}) <100 nM (IB, 2013a). In contrast, there was poor or no activity in other BRAF mutants or wt BRAF cell lines.

Dabrafenib given orally (PO) for 14 days at doses ranging from 0.1-300 mg/kg administered once daily (QD), twice daily (BID), or three times daily (TID) inhibited tumor growth in mice bearing $BRAF^{V600E}$ A375P F11s or Colo205 tumor xenografts. The effect was generally dose dependent up to 10 mg/kg/day (A375P F11s) or 30 mg/kg/day (Colo205), yielding 90-120% tumor reduction relative to untreated animals. However, cessation of treatment was associated with regrowth of the tumors. In A375P F11s melanoma xenografts, inhibition of pERK by >50% in the tumor was seen at doses of ≥3 mg/kg. Based on the single-dose studies, ~100 nM (52 ng/mL) dabrafenib in blood at 6 h post-dosing was needed for effective pharmacodynamic biomarker inhibition in the tumor. At repeated dosing of 30 mg/kg/day, the tumor pERK levels were reduced by >50% at 8 h after dosing (69% on Day 1 and 53% on Day 14). Levels of pERK returned to baseline 24 h post-dosing. Similar ↓pERK effects were seen in the ES-2 ovarian xenograft model, but pERK inhibition was weaker in the Colo205 xenograft model. Of note, concentrations of dabrafenib showing pharmacodynamic activity in xenografts did not cause a reduction in pERK/tERK levels in the normal intact brain.

5.6.1.1.2- Clinical Pharmacokinetics (PK) and Activity of Dabrafenib

Following single-dose oral administration of dabrafenib HPMC capsules, plasma concentrations peaked approximately 2.0 hours post-dose. Oral bioavailability is near complete (94.5%) relative to an intravenous (IV) microdose.

Dabrafenib is highly bound to plasma proteins (99.6%). Its volume of distribution after IV dosing is 45.5 L. Intravenous plasma clearance (12.0 L/hr) is low relative to liver blood

flow, suggesting a low hepatic extraction ratio drug. Median terminal half-life is approximately 8 hours after a single oral dose.

Three metabolites of dabrafenib were characterized and may contribute to activity. GSK2285403 (hydroxy-metabolite [M7]) PK paralleled that of dabrafenib, while the carboxy- (GSK2298683 [M4]) and desmethyl- (GSK2167542 [M8]) metabolites exhibited a longer $t_{1/2}$ (21-22 hours) and accumulated following repeat dosing. M7 is the most abundant, accounting for 54% of the three metabolites. Similar to dabrafenib concentrations, exposure for all metabolites showed a less than dose proportional increase with repeat dosing.

Fecal excretion was a major route of dabrafenib elimination in humans, accounting for 71.1% of the dose administered, and renal excretion accounted for about 23% of drug elimination, recovered as metabolites only.

Administration of dabrafenib with a high-fat, high-calorie meal reduced the oral bioavailability of dabrafenib when compared to the fasted state with a decrease in C_{max} and AUC of 51% and 31%, respectively, and delayed its absorption. Therefore, the current recommendation is to administer dabrafenib under fasting conditions, either 1 h before or 2 h after a meal.

Drug-drug interactions for dabrafenib:

Dabrafenib induces CYP3A4 and CYP2C9. Dabrafenib decreased the systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), and R-warfarin (a CYP3A4/CYP1A2 substrate). Co-administration of dabrafenib 150 mg twice daily for 15 days and a single dose of midazolam 3 mg (a CYP3A4 substrate) decreased midazolam AUC by 74%. Co-administration of dabrafenib 150 mg twice daily for 15 days and a single dose of warfarin 15 mg decreased the AUC of S-warfarin (a CYP2C9 substrate) by 37% and the AUC of R-warfarin (a CYP3A4/CYP1A2 substrate) by 33%.

In vitro studies show that dabrafenib is a substrate of CYP3A4 and CYP2C8 while hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Co-administration of dabrafenib 75 mg twice daily and ketoconazole 400 mg once daily (a strong CYP3A4 inhibitor) for 4 days increased dabrafenib AUC by 71%, hydroxy-dabrafenib AUC by 82%, and desmethyl-dabrafenib AUC by 68%. Co-administration of dabrafenib 75 mg twice daily and gemfibrozil 600 mg twice daily (a strong CYP2C8 inhibitor) for 4 days increased dabrafenib AUC by 47%, with no change in the AUC of dabrafenib metabolites. Dabrafenib is a substrate of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in vitro.

Pharmacodynamic effect of dabrafenib:

Median tumor pERK inhibition was 83.9% (range: 38.0 to 93.3%) in BRAF mutant melanoma subjects receiving doses of 70 to 200 mg BID. The relationship between exposure and % pERK inhibition was characterized using a maximum response (E_{max}) model with 100% maximum inhibition and IC_{50} of 134 ng/mL (95% CI: 92.7, 155) based on the sum of the potency-adjusted parent and active metabolite concentrations. A dose-related decrease in pERK was predicted with total daily doses <200 mg (100 mg BID) dabrafenib, with a plateau occurring beyond total daily doses of 200 mg thereafter.

Selection of the RP2D for dabrafenib monotherapy:

The single-agent MTD for dabrafenib was not reached. A dose of 150 mg BID was selected for further single-agent development, based on the following PK/pharmacodynamics, safety, and activity: a) dose increases beyond 150 mg BID yielded no increase in C_{max} and <50% increase in AUC; b) incidence and severity of AEs was similar at 100-300 mg BID; c) pERK target suppression was >80%; and d) the tumor response rate (RR) was 50% at 150 mg BID.

Antitumor Activity of Dabrafenib Monotherapy

Activity in patients with BRAF V600E or V600K melanoma in The FTIH monotherapy study (BRF112680). The study enrolled 114 patients with BRAF ^{V600} mutant melanoma in the dose escalation phase (Part 1), and 70 patients at the RP2D (150 mg BID) in Part 2. Within this study, a cohort of 10 patients with previously untreated asymptomatic brain metastasis was evaluated for intracranial response to dabrafenib (Long *et al.,* 2011). All patients had decreases in the size of the brain metastasis; three patients achieved complete radiographic resolution of brain lesions as well as reduction in extracranial disease. The response rates in patients treated at 150 mg BID are shown below.

Table 6. FTIH Monotherapy Study (BRF112680) Response Rates in Melanoma Patients

	Subgroup	Patient #	ORR
Part 1	V600E	77	50%
	V600K	14	20%
Part 2, Cohort A	V600E/K with brain mets	10	40%
	V600E/K without brain mets	20	55%

When dabrafenib was used at 50 mg BID (Part 2, Cohort C) in patients with BRAF ^{V600E} mutant melanoma, the response rate was only 17%.

Correlative studies in the phase 1 monotherapy trial:

Preliminary genomic analysis was performed on 37 patients with melanoma, using a Sequenom mutation analysis for 11 genes (AKT, BRAF, CDK4, CDKN2A, GNAQ, GNA11, Kit, MEK1, MEK2, and NRAS), and PTEN analysis by sequencing, comparative genomic hybridization (CGH), and multiplex ligation-dependent probe amplification (MPLA) (Nathanson *et al.,* 2011). Nine patients (24%) had PTEN genetic alterations including mutation, hemi-/homozygous deletion. PTEN deficiency was associated with lower responses (ORR of 11% and 54% in patients with and without PTEN alteration, respectively).

Phase III trial of dabrafenib versus chemotherapy in patients with advanced BRAFV600 mutant melanoma (BREAK3 Trial):

Patients with previously untreated, unresectable stage III or IV $BRAF^{V600E}$-mutated melanoma were randomized (3:1) and stratified by stage to dabrafenib (150 mg PO BID) or dacarbazine (DTIC) (1000 mg/m^2, IV, every 3 weeks [Q3W]). Of 250 patients 187 received dabrafenib and 63 received DTIC. The hazard ratio for PFS was 0.30 (95% CI: 0.18-0.53; $P<0.0001$), with median PFS of 5.1 months for dabrafenib and 2.7 for DTIC. OS data were immature, with 30 deaths reported. Confirmed RR was 53% for dabrafenib and 19% for DTIC. Benefits in PFS and RR were observed in all subgroups evaluated.

Activity in $BRAF^{V600E}$ mutant tumors other than melanoma:

In phase 1 trial, 18 patients had cancers other than melanoma: CRC (7), papillary thyroid cancer (PTC) (13), NSCLC (1) and ovarian cancer (1). Confirmed PRs were seen in one patient with CRC, and in 5 patients with PTC; the patient with NSCLC had an unconfirmed PR at 6 weeks. Eleven patients (6 with PTC and 5 with CRC) had stable disease (SD) as their best response; the ovarian cancer patient had SD for approximately 36 weeks.

Efficacy and safety data for dabrafenib in patients with Erdheim Chester Disease are not available. This will be the first therapeutic trial to address this.

5.6.1.1.3- Dabrafenib Safety Profile

A **Comprehensive Adverse Events and Potential Risks (CAEPR)** list using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms is included in appendix 2.

As of February 20, 2012, among 184 patients treated on the FTIH phase 1 trial, 99% experienced at least one adverse event (AE) (any grade). The most common (>20% of all subjects) AEs of any grade across all dosing cohorts in Part 1 and Part 2 were fatigue (42%), pyrexia (37%), headache (35%), nausea (34%), hyperkeratosis (33%), diarrhea (27%), arthralgia (25%), pain in extremity (25%), decreased appetite (24%), alopecia

(23%) and rash (23%).

Serious AEs (SAEs) were reported in 39% of patients, including SCC (12%), pyrexia (7%), and urinary tract infection (3%). Sixty-four patients are reported to have had study drug interrupted due to the occurrence of AEs. Pyrexia was the AE that led most frequently to a dose interruption. Fifteen patients reported a dose reduction due to the occurrence of AEs. There were no instances of discontinuation of study treatment due to AEs and no fatal AEs reported in the study among patients who received at least one dose of dabrafenib.

AEs of special interest:

The following events observed in dabrafenib monotherapy studies are discussed in detail because they may be a class effect of BRAF inhibitor compounds, have occurred at high frequency, and/or are potentially life-threatening.

Dermatologic effects: Rashes and other skin lesions, from hyperkeratosis to SCC, have been observed at the frequencies listed in Table 7.

Table 7. Dermatologic Side Effects of Dabrafenib in FTIH Study BRF112680

AE Term	Any Grade	Grade ≥3
Hyperkeratosis	61 (33)	0
Skin papilloma	46 (25)	1 (<1)
Rash	42 (23)	1 (<1)
Skin lesion	26 (14)	0
Actinic keratosis	21 (11)	0
Squamous cell carcinoma	22 (12)	21 (11)
Pruritis	22 (12)	0
Seborrheic keratosis	25 (14)	0
Acrochordon	19 (10)	0
Melanocytic nevus	19 (10)	0
Rash pruritic	11 (6)	0

Pre-malignant and malignant skin lesions: Cutaneous SCC and keratocanthoma were reported in 11% and 2%, respectively, of patients treated with dabrafenib in FTIH study BRF112680. SCC and proliferative skin toxicities are considered a class effect of BRAF inhibitors such as vemurafenib and sorafenib (Long *et al.,* 2011). SCC was treated with local excision, and treatment with dabrafenib was continued. Most SCCs of the skin have been localized and generally treated with curettage, and have been without significant clinical sequelae. Only one patient required a dose reduction in response to the event. The median onset of the first SCC occurred on Day 67 (range: Day 9-217).

Other treatment-emergent malignancies: Other treatment-emergent cutaneous malignancies such as basal cell carcinoma and new primary melanoma have been reported with BRAF inhibitors (Zelboraf, 2011).

Pyrexia: Across dabrafenib studies, all SAEs of pyrexia, influenza-like illness, cytokine release syndrome, systemic inflammatory response syndrome underwent clinical review for serious events of pyrexia complicated by hypotension, dehydration, circulatory collapse, severe rigors, or renal failure in the absence of another identifiable etiology (*i.e.*, infection).

Abnormal ejection fraction: Left ventricular ejection fraction (LVEF) changes were not observed in the early safety reviews of dabrafenib. However, these events are included in AEs of special interest because they are known side effects of several kinase inhibitors including imatinib, sunitinib, and lapatinib (Force *et al.*, 2007).

Cardiac valvular abnormalities: Data from preclinical studies suggested that dabrafenib has the potential to cause cardiac valve abnormalities. In a 28-day dog toxicology study, high doses (50 mg/kg/day; approximately 40-fold over the therapeutic dose) of dabrafenib in 1 dog (n=10) resulted in hypertrophy of the right atrio-ventricular valve (tricuspid valve). Therefore, this was monitored in clinical trials with echocardiograms.

Uveitis: Uveitis was reported at a frequency of 3.8% as an AE of vemurafenib in previously treated patients with BRAF V600 mutation-positive metastatic melanoma (Chapman *et al.*, 2011; Sosman *et al.*, 2010), and has been observed in patients receiving dabrafenib (incidence in study BRF112680 was 1%).

Renal failure: Cases of renal failure have been identified on clinical trials with a possible causal relationship to dabrafenib.

5.6.1.2- Clinical Experience with the Combination of Dabrafenib + Trametinib[25]

Data on 247 patients with metastatic melanoma and $BRAF^{V600}$ mutations participating in the phase 1/2 study of dabrafenib and trametinib, BRF113220, have been published (Flaherty *et al.*, 2012).

PK

Coadministration of dabrafenib 150 mg twice daily and trametinib 2 mg once daily resulted in no clinically relevant pharmacokinetic drug interactions.

RP2D for the combination of trametinib and dabrafenib

In the dose escalation portion (Part B) of study BRF113220, the MTD of the combination was not reached, and the RP2D was therefore 150/2 (Flaherty *et al.*, 2012). Pyrexia, chills,

and nausea were the most common reasons cited for dose reductions; pyrexia, chills, and decreased ejection fraction were the most common reasons cited for dose interruptions.

In the randomized, open-label, phase 2 portion (Part C) of the study, the incidence of certain AEs were lower with the combination as compared to single agent dabrafenib: cutaneous squamous-cell carcinoma (including keratoacanthoma) (7 vs. 19%), and rash (27 vs. 36%) (Flaherty *et al.*, 2012). On the other hand, the frequencies of pyrexia appeared increased (39 vs. 14%). The combination was also associated with an increased prevalence of MEK inhibitor-associated acneiform dermatitits (16 vs. 4%, with no grade 3 or 4 events reported). There was one death from sepsis in the 150/1 combination group, and there were three deaths in the combination 150/2 group (two from brain hemorrhage and one from pulmonary embolism); none of these events were considered to be related to a study drug. The incidences of main AEs (all grades) observed in Part C of the trial are presented in the table below as patients (percent).

Table 8. Adverse Events in Patients Treated with Dabrafenib Alone and in Combination with Trametinib

Adverse Event	Dabrafenib Monotherapy (n=53)	Combination 150/1 (n=54)	Combination 150/2 (n=55)
Pyrexia	14 (26)	37 (69)	39 (71)
Nausea	11 (21)	25 (46)	24 (44)
Vomiting	8 (15)	23 (43)	22 (40)
Diarrhea	15 (28)	14 (26)	20 (36)
Rash	19 (36)	11 (20)	15 (27)
Hyperkeratosis	16 (30)	3 (6)	5 (9)
Cutaneous squamous cell carcinoma	10 (19)	1 (2)	4 (7)
Alopecia	18 (34)	5 (9)	3 (5)
Skin papilloma	8 (15)	4 (7)	2 (4)
Decreased ejection fraction	0	2 (4)	5 (9)
Cardiac failure	0	1 (2)	0
Hypertension	2 (4)	2 (4)	5 (9)
Chorioretinopathy	0	0	1 (2)
Neutropenia			(11)
Acneiform dermatitis	(4)	(11)	(16)

Activity

Efficacy analyses were performed in the intention-to-treat population of the phase 2 portion (Part C) of study BRF113220, with a median follow-up of 14.1 months (Flaherty *et al.*,

2012). All major efficacy endpoints were improved, including PFS, 12-month PFS, ORR, and duration of response. Endpoint values as assessed by site investigators for this portion of the study are presented in the table below.

Table 9. Endpoint Analysis of Patients Treated with Dabrafenib Alone and in Combination with Trametinib

End Point	Dabrafenib Monotherapy (n=54)	Combination 150/1 (n=54)	Combination 150/2 (n=54)
Progression-free Survival – months Median (95% CI)	5.8 (4.6-7.4)	9.2 (6.4-11.0)	9.4 (8.6-16.7)
Progression-free Survival at 12 mo. % (95% CI)	9 (3-20)	26 (15-39)	41 (27-54)
CR or PR Patients (% [95% CI])	29 (54 [40-67])	27 (50 [36-64])	41 (76 [62-86])
Duration of response Median months (95% CI)	5.6 (4.5-7.4)	9.5 (7.4-NA)	10.5 (7.4-14.9)

5.6.1.3- Trametinib Dimethyl Sulfoxide (GSK1120212B, MEKINIST)[25]

The RAF-MEK-ERK pathway plays a critical role in multiple cellular functions. Activation of the pathway can result from activating mutations of the upstream receptor tyrosine kinases (RTKs) and RAS, or upregulation/mutations in RAF and MEK. Upon activation, RAF acts as the MAPK kinase kinase and activates MAPKK (MEK1/2), which in turn catalyze activation of the effectors ERK1/ERK2. Once activated, ERK1/2 translocate into the nucleus and phosphorylate a number of effector proteins and transcriptional factors that regulate cell proliferation, motility, differentiation, and survival. Trametinib is one of the several MEK inhibitors in clinical development.

Experience to date indicates that MEK is a valid target. In a phase III trial comparing trametinib with dacarbazine or paclitaxel in patients with BRAF V600E or V600K mutant metastatic melanoma, trametinib demonstrated a significantly better response rate, progression-free survival, and overall survival (Flaherty *et al.*, 2012). However, single agent activities are limited. Extensive research is underway to identify patient selection markers and develop rational combination strategies. Preclinical studies have provided strong rationale and proof of principle for combining MEK inhibitors with RTK inhibitors (EGFR or IGF-1R) (Gopal *et al.,* 2010; Ebi *et al.,* 2011), PI3K/AKT inhibitors (Engelman *et al.,* 2008; Hoeflich *et al.,* 2009), and mTOR inhibitors. On the other hand, the optimal dose/schedule and patient selection criteria for combination regimens have not been defined. Phase 1 results for a number of combinations have been reported, including AZD6244 + MK2206 (Tolcher *et al.,* 2011) and GDC-0973 + GDC-094 (MEK+ PI3K

inhibitor) (Bendell *et al.,* 2011).

5.6.1.3.1- Mechanisms of Action and Preclinical Data with Trametinib

Trametinib is a dimethyl sulfoxide (DMSO) solvate compound (ratio 1:1) with potent, allosteric and ATP non-competitive inhibition of MEK1/2 (IC_{50} of 0.7 and 0.9 nM against MEK1 and MEK2, respectively) (Gilmartin *et al.,* 2011). Trametinib inhibited MEK1/2 kinase activity and prevented RAF-dependent MEK phosphorylation (S217 for MEK1), producing prolonged pERK1/2 inhibition. Trametinib showed better potency against unphosphorylated MEK1/2 (u-MEK1/2) when compared with preactivated diphosphorylated MEK (pp-MEK), suggesting that u-MEK affords a higher affinity binding site for trametinib than does pp-MEK.

The specificity of trametinib was confirmed against a panel of 183 kinases, including MEK5 (the closet kinase homolog to MEK1/2), CRAF, BRAF, ERK1, and ERK2 (Yamaguchi *et al.,* 2011). Trametinib demonstrated equal potency against activated MEK1- and MEK2-mediated phosphorylation of ERK (sequence identity of 85% across the whole protein and 100% in the active site for humans). Trametinib demonstrated preferential inhibition of RAF-mediated MEK1 activation (IC_{50} = 0.60 nM) over pMEK1 kinase activity (IC_{50} = 13 nM) (Investigator's Brochure, 2012a).

BRAF-mutant Colo205, A375P F11s, and HT-29 human tumor xenograft mouse models showed the most significant mean tumor growth inhibition (TGI) (80% to 87%) at 3.0 mg/kg trametinib, with multiple complete and partial tumor regressions. In the Colo205 model, tumor regression was observed even at a dose of 0.3 mg/kg (Yamaguchi *et al.,* 2011). Two KRAS-mutant xenograft models, HCT-116 and A549, also showed significant TGI (83% and 75%) but without significant tumor regressions (Gilmartin *et al.,* 2011). As predicted by cell proliferation assays, tumor xenograft lines with wild-type (wt) RAF/RAS (PC3, BxPC3, and BT474) were much less sensitive, showing only modest TGI (44-46%) with no tumor regressions.

Pharmacodynamic studies were performed in mice treated with trametinib for 14 days (Gilmartin *et al.,* 2011). In the A375P F11s xenograft model, the first dose of trametinib (3 mg/kg) significantly reduced pERK for more than 8 hours on Day 1. pERK inhibition was more sustained (over 24 hours) after the Day 7 dose, probably due to an increase in the steady-state levels of trametinib after repeated doses. The average C_{max} in blood was 1,410 nM on Day 7, with an estimated half-life ($t_{1/2}$) of 33 hours. In addition, immunohistochemistry (IHC) also confirmed inhibition of cell proliferation (reduced Ki67) and G1 cell cycle arrest (elevated p27Kip1/CDKN1B) following 4 days of treatment.

5.6.1.3.2- Clinical Pharmacokinetics (PK) and Activity of Trametinib

FTIH Phase 1 Trial of Trametinib Monotherapy (MEK111054)

There are 3 parts in this ongoing study. Part 1: The dose-escalation portion involves administration of trametinib (repeat doses of 0.125 mg to 4.0 mg) to patients with solid tumors or lymphoma in one of three schedules - (1) QD for 21 days followed by 7 days without drug, (2) loading dose on Day 1 or Day 1-2, followed by QD with the designated dose, or (3) QD dosing without a drug holiday. Part 2: cohort expansion at the recommended phase 2 dose (RP2D) for pancreatic cancer, melanoma, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), or any BRAF mutation-positive cancer. Part 3: expansion to characterize the biologically active range of trametinib via analysis of pharmacodynamic biomarkers (biopsies or FDG-PET).

The dose escalation part and some of the cohort expansion components have been completed. The MTD of trametinib was established as 3 mg QD, but the recommended phase 2 dose (RP2D) was chosen at 2 mg QD based on tolerability of repeated cycles (Infante *et al.,* 2010).

PK and metabolism of trametinib:

PK measurements were conducted under fasting conditions. After a single dose (Day 1), AUC_{0-24} and C_{max} values were dose-proportional up to 6 mg, lower than dose proportional following 8 mg, and greater than dose proportional following the 10 mg dose. Median T_{max} was 1.5 hours.

After repeat doses (Day 15), trametinib accumulated with a mean accumulation ratio of 6.6 at the RP2D of 2 mg QD. Between-subject variability in exposure ranged from 27-50% for C_{max} and 20-41% for AUC_{0-24} across all dosing regimens. The effective $t_{1/2}$ was approximately 4.5 days, and steady state was reached by approximately Day 15. Trametinib had a small peak:trough ratio of ~2 (Infante *et al.,* 2010). At 2 mg QD on Day 15, mean AUC_{0-24} was 376 ng•h/mL and C_{max} 23 ng/mL, and the mean trough concentrations ranged from 10.0 to18.9 ng/mL. The long half-life and small peak:trough ratio of trametinib allowed constant target inhibition within a narrow range of exposure.

Drug-drug interactions:

Trametinib is metabolized predominantly via deacetylation (non-cytochrome P450 [CYP450]-mediated) with secondary oxidation or in combination with glucuronidation biotransformation pathways (Investigator's Brochure, 2012a). The deacetylation is likely mediated by hydrolytic esterases, such as carboxylesterases, or amidases. Based on *in vitro* studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP3A4. Although trametinib was found to be an *in vitro* inhibitor of CYP2C8, CYP2C9, and 2C19; inducer of CYP3A4; and inhibitor of transporters (OATP1B1, OATP1B3, P-

glycoprotein [P-gp], and breast cancer resistance protein [BCRP]), its low efficacious dose, and low clinical systemic concentration (22.2 ng/mL or 0.04 mcM at 2 mg) relative to the *in vitro* inhibition/induction potency suggests an overall low potential for drug-drug interactions.

Pharmacodynamic effect and biomarkers:

The relationship between dose and tumor biomarkers such as pERK, Ki67, and p27, were evaluated in patients with BRAF or NRAS mutation-positive metastatic melanoma (Investigator's Brochure, 2012a). In general, increasing exposures and/or doses provided greater pharmacodynamic effects. The median change observed at a dose of 2 mg QD was 62% inhibition of pERK, 83% inhibition of Ki67, and a 175% increase in p27.

Antitumor Activity in the FTIH phase 1 trial:

In the FTIH phase 1 trial, 14 patients with BRAF-mutant melanoma received trametinib at 2 mg QD. The overall objective response rate (ORR) was 43% (6/14), including 2 complete responses (CRs) (Investigator's Brochure, 2012a). In 9 patients with BRAF wt melanoma, 2 patients achieved a partial response (PR), and 3 stable disease (SD) (Infante *et al.,* 2010). In 26 evaluable pancreatic cancer patients, there were 2 PRs (1 PR was KRAS mutation-positive) and 11 SD (2 achieved ≥20% tumor reduction) (Messersmith *et al.,* 2011). Among the 27 CRC patients (without selection of RAS or RAF mutations), 8 SD were observed.

Antitumor Activity in Melanoma

Phase 3 trial of trametinib vs. chemotherapy in advanced V600 mutant melanoma:

In a phase 3 trial, patients with unresectable stage IIIC or IV cutaneous melanoma with a BRAF V600E or V600K mutation were randomized (2:1) to trametinib (2 mg, PO, QD) or chemotherapy (dacarbazine or paclitaxel) (Flaherty *et al.*, 2012; MEKINIST Package Insert, 2013). There were 322 patients in the intention-to-treat (ITT) population, of whom 273 (85%) were in the primary efficacy population (patients with $BRAF^{V600E}$-positive cancer who did not have brain metastases at baseline). Of the patients, 214 were randomized to receive trametinib, and 108 were randomized to receive chemotherapy. Investigator-assessed efficacy data are summarized as follows:

Table 10. Response of Melanoma Patients to Trametinib Compared with DTIC Chemotherapy

	Trametinib (n=214)	**Chemotherapy (DTIC) (n=108)**
PFS Median, months (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
HR (95% CI)	0.47 (0.34, 0.65)	
P value (log-rank test)	*P*<0.0001	
Confirmed Tumor Responses		
Objective Response Rate (95% CI)	22% (17, 28)	8% (4, 15)
CR, n (%)	4 (2%)	0
PR, n (%)	43 (20%)	9 (8%)
Duration of response Median, months (95% CI)	5.5 (4.1, 5.9)	NR (3.5, NR)
CI = confidence interval; CR = complete response; HR = hazard ratio; NR = not reached; PFS = progression-free survival; PR = partial response		

The 6-month OS rate was 81% in the trametinib group and 67% in the chemotherapy group. Mature data on OS are pending.

Experience with Trametinib in Metastatic Melanoma Following BRAF Inhibitor Therapy

The clinical activity of single-agent trametinib was evaluated in a single-arm, multicenter, international trial in 40 patients with BRAF V600E or V600K mutation-positive, unresectable, or metastatic melanoma who had received prior treatment with a BRAF inhibitor. All patients received trametinib at a dose of 2 mg PO QD until disease progression or unacceptable toxicity. None of the patients achieved a confirmed PR or CR.

Antitumor Activity of Trametinib in Cancer Other Than Melanoma

In a phase 1/2 monotherapy study, acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) patients were given trametinib at dose levels from 1-2 mg QD. Drug-related

AEs in 45 patients were similar to that observed in patients with solid tumors, and 2 mg PO QD was selected for further investigation in this patient population. Twelve patients (23%) withdrew due to an AE, including cardiac failure (2) and infection (2). Efficacy was reported in 39 patients (Borthakur *et al.,* 2010). The best response in 13 patients with KRAS or NRAS mutations included 3 CRs (23%), 7 SD (54%), and 1 PD (progressive disease) (5%). In 26 patients with wild-type RAS or an unknown mutation, there were 2 PRs (8%).

In a multicenter phase 2 study, NSCLC patients with KRAS mutant tumors were randomized 2:1 to receive trametinib (2 mg QD) or docetaxel (75 mg/m^2 IV every 3 weeks) (Blumenschein *et al.*, 2013). A total of 134 pts were randomized to trametinib (89) or docetaxel (45); 129 patients had KRAS-mutant NSCLC. The hazard ratio for PFS was 1.14 (95% CI, 0.75-1.75; *P*=0.5197) with a median PFS of 11.7 versus 11.4 weeks for trametinib versus docetaxel. The overall response rate (ORR) was 12% for trametinib and 12% for docetaxel.

In a double-blind, phase 2 study evaluating the combination of gemcitabine with trametinib, untreated pancreatic cancer patients were randomized to receive gemcitabine (1000 mg/m2 weekly ×7 for 8 weeks, then weekly ×3 every 4 weeks) plus either trametinib 2mg or placebo QD (Infante *et al.*, 2013). Median OS was 8.4 months with trametinib compared to 6.7 months with placebo. Median PFS was 16 weeks versus 15 weeks, and ORRs and median duration of responses were 22% and 23.9 weeks and 18% and 16.1 weeks on trametinib and placebo; the median OS and ORR in the subgroup of patients with KRAS mutations (143/160) was similar to OS and ORR for all randomized patients.

Efficacy and safety data for trametinib in patients with Erdheim Chester disease are not available. This will be the first therapeutic trial that will address this.

5.6.1.3.3- Trametinib Safety Profile

A **Comprehensive Adverse Events and Potential Risks (CAEPR)** list using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms is included in appendix 2.

Based on available AE data from clinical studies involving trametinib to date, the most common toxicities are rash and diarrhea. Rash and diarrhea are common, class-effect toxicities for MEK inhibitors. In addition, visual impairment and left ventricular ejection fraction (LVEF) reduction, although observed at lower frequencies, are also considered class-effect toxicities as they have been observed with trametinib as well as other MEK inhibitors.

AEs of special interest:

Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs, and pneumonitis are considered AEs of special interest because they are either known class effects (*i.e.*, have been observed with other MEK inhibitors) or are potentially life-threatening (Investigator's

Brochure, 2012a).

Skin Toxicities: Rash was a common AE observed across different dose levels and in different combinations. The majority of rash observed with trametinib was acneiform and occur most frequently on the face, scalp, chest, and upper back. However, serious skin toxicities can occur and lead to infection and hospitalization. At the 2 mg dose, rash was seen in 48% to 91% of patients in different trials. The majority of rash AEs were grades 1 or 2 (68% to 80%); 1% to 18% of patients experienced grade 3 rash AEs, and one patient had a grade 4 rash AE.

In a randomized phase 3 trial of trametinib vs. chemotherapy, the overall incidence of skin toxicity (including rash, dermatitis, acneiform rash, palmar-plantar erythrodysesthesia syndrome, and erythema) was 87% in patients treated with trametinib and 13% in chemotherapy-treated patients. Severe skin toxicity occurred in 12% of patients on the trametinib arm, most commonly for secondary infections of the skin. The median time to onset of skin toxicity was 15 days (range: 1 to 221 days), and median time to resolution was 48 days (range: 1 to 282 days). Dose reduction was required in 12% for skin toxicities, and permanent discontinuation of trametinib was required in 1% of patients.

Refer to dose modification guidelines for skin toxicities.

Diarrhea: At the 2 mg monotherapy dose, 28% to 58% of patients in three trials had diarrhea. Of 219 patients with diarrhea at this dose, the majority of diarrhea AEs were grade 1 or 2 in severity (28% to 56% of all study patients); 6 patients had grade 3 diarrhea, and none had grade 4 diarrhea.

Visual disorders: At the 2 mg monotherapy dose, 6% to 21% of the patients in three trials experienced visual disorders. Of the 62 total patients experiencing visual disorders at this dose level, the majority of visual disorders were grades 1 or 2 (6% to 20% of all study patients); five patients experienced grade 3 visual disorders, and one patient experienced a grade 4 visual disorder.

- *Central serous retinopathy (CSR) with Retinal Pigment Epithelial Detachment (RPED):* CSR is a class side effect of MEK inhibitors. Across all clinical trials, the incidence of RPED was 0.8% (14/1749). In the randomized trial with trametinib vs. chemotherapy where ophthalmologic examinations including retinal evaluation pretreatment and at regular intervals during treatment, one patient (0.5%) receiving trametinib developed RPED.

  Retinal detachments were often bilateral and multifocal, occurring in the macular region of the retina. RPED led to reduction in visual acuity that resolved after a median of 11.5 days (range: 3 to 71 days) following the interruption of trametinib, although Ocular Coherence Tomography (OCT) abnormalities persisted beyond a month in at least several cases. Perform ophthalmological evaluation at any time a patient reports

visual disturbances and compare to baseline. Refer to dose modification guidelines for visual disturbance for management and dose interruption/discontinuation.

- *Retinal vein occlusion (RVO):* Across all clinical trials, the incidence of RVO was 0.2% (4/1749). An RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma. It is recommended to urgently (within 24 hours) perform ophthalmological evaluation for patient-reported loss of vision or other visual disturbances, and permanently discontinue trametinib in patients with documented retinal vein occlusion (see Dosage Modification guidelines).

Hepatic disorders: Abnormalities of liver enzymes and bilirubin have been observed with administration of trametinib. However, assessment of these cases was often confounded by co-morbid conditions (such as biliary obstruction), concomitant use of other potentially hepatotoxic drugs, and liver metastases. At the 2 mg monotherapy dose, 10% to 19% of patients in three trials had LFT abnormalities. Of the 56 total patients with LFT changes, the majority were grade 1 or 2 in severity (7% to 15% of all study patients); 12 had grade 3 events, and 3 patients had grade 4 events.

Cardiac-related AEs: At the 2 mg monotherapy dose across trials, 11% of patients developed evidence of cardiomyopathy (decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF ≥10% below baseline), and 5% demonstrated a decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF of ≥20% below baseline. Most cardiac AEs are grade 1 or grade 2, but grade 4 or 5 cardiac AEs have rarely been reported.

In the phase 3 trial of trametinib vs. chemotherapy in patients with melanoma (MEK114267), cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased LVEF) occurred in 7% (14/211) of patients treated with trametinib, and in no patients in the chemotherapy arm. Cardiomyopathy was identified within the first month of treatment in five of these 14 patients; median onset of cardiomyopathy was 63 days (range: 16 to 156 days). Cardiomyopathy resolved in 10 of these 14 (71%) patients. Cardiac monitoring should be included in trametinib protocols, to include LVEF assessment by echocardiogram or MUGA scan at baseline, one month after initiation of trametinib and then at 2- to 3-month intervals while on treatment. Dose modification guidelines for cardiac AEs should be followed in the event of LVEF decline or symptomatic cardiac AEs.

Pneumonitis (interstitial lung disease): Pneumonitis or interstitial lung disease was reported in 1.8% of patients. In the randomized phase III trial for trametinib vs. chemotherapy, 2.4% patients (5/211) developed pneumonitis, all of whom required hospitalization. Median onset of the first presentation of pneumonitis was 160 days (range: 60-172 days).

Embryofetal toxicity: Based on its mechanism of action, trametinib can cause fetal harm when administered to a pregnant woman. Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended clinical dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Incidence of common AEs reported from a phase III trial of trametinib vs. chemotherapy in patients with advanced melanoma:

Patients with abnormal LVEF, history of acute coronary syndrome within 6 months, or current evidence of Class II or greater congestive heart failure (New York Heart Association) were excluded from this trial. Selected adverse reactions (AR) occurring in patients receiving trametinib as compared to patients in the chemotherapy arm are listed as below:

Table 11. Selected Adverse Reactions (ARs) Occurring in ≥10% of Patients Receiving Trametinib AND at a Higher Incidence than in the Chemotherapy Arm.

Events are listed only if they were high in the trametinib arm compared with chemotherapy by ≥5% in overall incidence or by ≥2% grade 3 or 4 AEs.

	Trametinib (n=211)		**Chemotherapy (n=99)**	
Adverse Reactions	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Skin and subcutaneous tissue disorders				
Rash	57	8	10	0
Dermatitis acneiform	19	<1	1	0
Dry skin	11	0	0	0
Pruritis	10	2	1	0
Paronychia	10	0	1	0
Gastrointestinal disorders				

Diarrhea	43	0	16	2
Stomatitis	15	2	2	0
Abdominal pain	13	1	5	1
Vascular disorders				
Lymphedema	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage	13	<1	0	0

Table 12. Percent-patient Incidence of Laboratory Abnormalities Occurring at a Higher Incidence in Patients Treated with Trametinib Versus Chemotherapy.

Events are listed only if between-arm differences were ≥5% [all grades] or ≥2% [grades 3 or 4].

	Trametinib (n=211)		**Chemotherapy (n=99)**	
Preferred term	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Increased aspartate aminotransferase (AST)	60	2	16	1
Increased alanine aminotransferase (ALT)	39	3	20	3
Hypoalbuminemia	42	2	23	1
Anemia	38	2	26	3
Increased alkaline phosphatase	24	2	18	3

Other clinically important adverse reactions observed in ≤10% of patients (n=329) treated with trametinib were: nervous system disorders (dizziness, dysgeusia), ocular disorders (blurred vision, dry eye), infections and infestations (folliculitis, rash pustular, cellulitis), cardiac disorders (bradycardia), gastrointestinal disorders (xerostomia), and

musculoskeletal and connective tissue disorders (rhabdomyolysis).

5.6.1.4- Clinical Experience and Safety Profile with the Combination of Trametinib + Dabrafenib

Comprehensive Adverse Events and Potential Risks (CAEPR) lists using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms for dabrafenib and for trametinib are included in Appendix 2 of the protocol.

Based on available AE data from clinical studies involving **dabrafenib** to date, the most common drug-related AE was hyperkeratosis (29%). Other commonly reported (>15%) drug-related AEs included alopecia, arthralgia, fatigue, skin papilloma, pyrexia, and rash (IB, 2013).

Based on available AE data from clinical studies involving **trametinib** to date, the most common toxicities are rash and diarrhea. Rash and diarrhea are common, class-effect toxicities for MEK inhibitors. In addition, visual impairment and left ventricular ejection fraction (LVEF) reduction, although observed at lower frequencies, are also considered class-effect toxicities as they have been observed with trametinib as well as other MEK inhibitors.

Common Adverse Events of Dabrafenib-Trametinib Combination vs. Dabrafenib Monotherapy. The phase 2 portion of study BRF113220 (referred to as Part C) included 3 arms: dabrafenib 150 mg BID + trametinib 2 mg QD, dabrafenib 150 mg BID + trametinib 1 mg QD, and single-agent dabrafenib 150 mg BID. The most common AE resulting in permanent discontinuation was pyrexia (4%). AEs led to dose reductions in 49% and dose interruptions in 67% of patients treated with dabrafenib in combination with trametinib. The table below presents selected adverse reactions and treatment-emergent laboratory abnormalities in this study.

Table 13-Selected AEs and Laboratory Abnormalities Occurring in ≥10% at (All Grades) or ≥5% (Grades 3 or 4) of Patients Treated With Dabrafenib in Combination With Trametinib

Adverse Reaction or Laboratory Abnormality	Dabrafenib + Trametinib 2mg (n=55)		Dabrafenib + Trametinib 1mg (n=54)		Dabrafenib (n=53)	
	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4
General disorders and administrative site conditions						
Pyrexia	71	5	69	9	26	0
Chills	58	2	50	2	17	0
Fatigue	53	4	57	2	40	6
Edema peripheral[b]	31	0	28	0	17	0
Skin and subcutaneous tissue disorders						
Rash[c]	45	0	43	2	53	0
Night sweats	24	0	15	0	6	0
Dry skin	18	0	9	0	6	0
Dermatitis acneiform	16	0	11	0	4	0
Actinic keratosis	15	0	7	0	9	0
Erythema	15	0	6	0	2	0
Pruritis	11	0	11	0	13	0
Gastrointestinal disorders						
Nausea	44	2	46	6	21	0
Vomiting	40	2	43	4	15	0
Diarrhea	36	2	26	0	28	0
Metabolism and nutritional disorders						

Table 13-Selected AEs and Laboratory Abnormalities Occurring in ≥10% at (All Grades) or ≥5% (Grades 3 or 4) of Patients Treated With Dabrafenib in Combination With Trametinib

Adverse Reaction or Laboratory Abnormality	Dabrafenib + Trametinib 2mg (n=55)		Dabrafenib + Trametinib 1mg (n=54)		Dabrafenib (n=53)	
	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4
Decreased appetite	22	0	30	0	19	0
Dehydration	11	0	6	2	2	0
Vascular disorders						
Hemorrhage[d]	16	5	11	0	8	2
Renal and urinary disorders						
Renal failure[e]	7	7	2	0	0	0
Hematology						
Leukopenia	62	5	46	4	21	0
Neutropenia	55	13	37	2	9	2
Liver function tests						
Increased AST	60	5	54	0	15	0
Increased alkaline phosphatase	60	2	67	6	26	2
Increased ALT	42	4	35	4	11	0
Hyperbilirubinemia	15	0	7	4	0	0
Chemistry						

Table 13-Selected AEs and Laboratory Abnormalities Occurring in ≥10% at (All Grades) or ≥5% (Grades 3 or 4) of Patients Treated With Dabrafenib in Combination With Trametinib

Adverse Reaction or Laboratory Abnormality	Dabrafenib + Trametinib 2mg (n=55)		Dabrafenib + Trametinib 1mg (n=54)		Dabrafenib (n=53)	
	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4
Hyperglycemia	58	5	67	6	49	2
Hyponatremia	55	11	48	15	36	2
Hypophosphatemia	47	5	41	11	40	0
Increased creatinine	24	5	20	2	9	0

[a] NCI CTCAE v4.

[b] Includes the following terms: peripheral edema, edema, and lymphedema.

[c] Includes the following terms: rash, rash generalized, rash pruritic, rash erythematous, rash popular, rash vesicular, rash macular, rash maculo-papular.

[d] Includes the following terms: brain stem hemorrhage, cerebral hemorrhage, gastric hemorrhage, epistaxis, gingival hemorrhage, hematuria, vaginal hemorrhage, hemorrhage intracranial, eye hemorrhage, and vitreous hemorrhage.

[e] Includes the following terms: renal failure and renal failure acute.

AEs of special interest:

The following events observed with dabrafenib monotherapy and for dabrafenib plus trametinib are discussed in further detail because they may represent a class effect of BRAF and/or MEK inhibitor compounds, and/or are potentially life-threatening. AEs of special interest associated with dabrafenib or trametinib individually are listed in the table below:

Table 14

AEs of special interest that are associated with dabrafenib (BRAF category AEs) are:	AEs of special interest that are associated with trametinib (MEK category AEs)
• Skin-related toxicities • Pyrexia	• Skin-related toxicities (e.g., rash – generalized, macular, maculopapular, pruritic, erythematous, etc; dermatitis acneiform;

• Malignancies • Renal failure (renal failure, renal failure acute) • Uveitis • Hyperglycemia • Pancreatitis	erythema; skin exfoliation • Diarrhea • Ocular events (e.g., RVO, RPED (previously termed CSR)) • Hepatic events (e.g., aspartate aminotransferase [AST], ALT, and blood bilirubin increased) • Cardiac-related events (e.g., LVEF decreased and left ventricular dysfunction) • Hypertension • Pneumonitis (pneumonitis, interstitial lung disease) • Hemorrhages

In general, the overall profile of "AEs of special interest" observed with the combination of trametinib-dabrafenib is consistent with the known profiles of each separate drug, the most notable differences being the increase in pyrexia and the decrease in skin-related toxicities with combination therapy relative to monotherapy.

For "MEK-related AEs of special interest," the overall incidence in the dabrafenib-trametinib combination arm in trial BRF113220 was 91%, which was similar to the incidence reported with trametinib ISS monotherapy (94%), but higher than the incidence in the dabrafenib alone arm. However, MEK-related skin toxicities, diarrhea and hypertension appeared to be lower in the combination arm, as compared with the trametinib-only treated population. The incidence rate of ocular events was higher relative to the trametinib ISS population.

For "BRAF-related AEs of special interest," the incidence of any event in combination arm was higher (84%) than either the Dabrafenib ISS population (49%) or the trametinib ISS population (19%). This increase is predominantly due to the increased incidence of pyrexia observed with combination treatment. Also noted were an increase in renal failure and a decrease in cuSCC and PPES when comparing the combination to dabrafenib ISS population.

The following sections provide more detailed description of the AEs of Special Interest.

Dermatologic toxicities (dabrafenib or dabrafenib-trametinib):

Dabrafenib monotherapy has been associated with skin-related toxicities including hyperkeratosis, skin papilloma, rash, seborrheic keratosis, acrochordon as well as rash and pruritis and cutaneous squamous cell carcinoma.

With the combination of dabrafenib-trametinib at 150/2 (Part C of the phase II trial), skin-related toxicity occurred in 65% of subjects (IB, 2013). This incidence was lower than observed in the trametinib ISS population (88%, 288 out of 329 subjects). The most frequent skin-related toxicities (affecting >10% treated with combination) were rash,

dermatitis acneiform, erythema, and rash generalized. The incidence and severity of the majority of skin-related toxicities and especially those most often seen with either trametinib- or dabrafenib therapy alone appear to be reduced when both compounds are combined.

Malignancies (dabrafenib or dabrafenib-trametinib**):**

Cutaneous SCC and keratoacanthomas*:* SCC and proliferative skin toxicities are considered a class effect of BRAF inhibitors such as vemurafenib and sorafenib (Long *et al.,* 2011). SCC was treated with local excision, and treatment with dabrafenib was continued. Most SCCs of the skin have been localized and generally treated with curettage, and have been without significant clinical sequelae.

Across clinical trials of dabrafenib monotherapy (n=586), the incidence of cutaneous SCC was 11%. Of those patients who developed new SCC, approximately 33% developed one or more SCC with continued administration of dabrafenib.

In randomized trial with dabrafenib vs. dabrafenib-trametinib combination (BRF113220), the incidence of cutaneous SCC/keratocanthoma was statistically lower with150/2 combination therapy relative to dabrafenib alone (7 vs. 19%). The median time to the first occurrence of keratoacanthoma/cuSCC was 152 days in the combination treatment group as compared to 30.5 days in the dabrafenib alone arm.

New primary malignant melanoma: In the randomized trial for dabrafenib-trametinib combination (BRF113220), new primary melanoma occurred in 2% (1/53) on dabrafenib monotherapy [similar to the dabrafenib ISS population (1%)] and in none of 55 patients receiving dabrafenib + trametinib (IB, 2013). The overall frequency of new primary melanomas observed with dabrafenib treatment approximates that expected for untreated subjects with antecedent melanoma.

Other treatment-emergent malignancies: Non-cutaneous secondary malignancies have also been reported in patients receiving dabrafenib or dabrafenib-trametinib combination. In patients receiving dabrafenib-trametinib combination, five cases out of 365 subjects (1%) were identified as having non-cutaneous malignancies: KRAS mutation-positive pancreatic adenocarcinoma (n=1), recurrent NRAS mutation-positive CRC (n=1), head and neck carcinoma (n=1), glioblastoma (n=1), and pre-existing renal cell carcinoma (n=1) (FDA label). No increase was detected in the overall frequency of treatment emergent malignancies in melanoma subjects receiving dabrafenib and trametinib treatment in Study BRF113220 as compared to the dabrafenib safety population. Dabrafenib should be permanently discontinued for RAS mutation-positive non-cutaneous malignancies.

Pyrexia (dabrafenib or dabrafenib-trametinib): Pyrexia and pyrexia-related events,

including influenza-like illness, cytokine release syndrome, and systemic inflammatory response syndrome are common side effects associated with dabrafenib. In dabrafenib- trametinib combination study BRAF113220 Part C, pyrexia and related events in the combination arm (150/2) were increased in frequency and severity (76%; 5% grade 3, no grade 4), as compared with dabrafenib monotherapy ISS population (33%; 2% grade 3, no grade 4). Eleven percent of subjects in the combination group required hospitalization for episodes of serious pyrexia (IB, 2013). Approximately 50% of the pyrexia-related events in the Part C 150/2 arm resulted in dose interruption and/or dose reduction, a higher proportion than in the dabrafenib ISS population (15% to 30%). The majority of subjects (>80%) who dose-reduced dabrafenib due to AEs were able to be dose re-escalated.

All SAEs of pyrexia-related events (pyrexia, influenza-like illness, cytokine release syndrome, and systemic inflammatory response syndrome) were manually reviewed to identify cases described as having experienced **serious non-infectious febrile events** with complications of hypotension, dehydration, severe rigors/chills, or renal failure in the absence of another identifiable etiology (*e.g.*, infection). Ten such subjects were identified among 404 subjects (2.5%) in the entire combination therapy population as compared to 1% in the dabrafenib ISS population; 9 of these subjects were hospitalized. All of these subjects required dose interruption(s) and/or dose modification(s); one subject permanently discontinued study drug after experiencing fever, muscle weakness, dehydration, and hyponatremia. All subjects responded to symptomatic therapy with either NSAIDs, paracetamol, or corticosteroids and best supportive care including IV fluids.

Renal failure (dabrafenib or dabrafenib-trametinib): Renal failure was observed in the dabrafenib ISS population (<1%; <1% grade 3/4) and trametinib ISS population (2%; no grade 3, <1% grade 4), and was increased in incidence and severity in the combination arm in study BRF113220 (7%, all grade 3) (IB, 2013). Most cases of acute renal failure presented as a secondary event in the setting of pyrexia where dehydration appeared to be a contributing factor and/or in concert with other risk factors such as hemolytic uremic syndrome (HUS), antibiotic toxicity, or hypercalcemia. There was one case of advanced renal failure which may have been drug-induced but whose precise etiology was not clear. The renal events led to permanent discontinuation of study drugs in one subject, and to dose interruptions in three subjects.

Hypertension (dabrafenib-trametinib): Hypertension has been associated with trametinib therapy. In the combination study of dabrafenib-trametinib, the combination arm had a higher rate of hypertension compared to the dabrafenib ISS population (9% vs. 2%); however, this rate was lower than that in the trametinib ISS population (15%) (IB, 2013).

In either the combination or the dabrafenib monotherapy population, there were no SAEs related to hypertension, and hypertension did not lead to treatment discontinuation, dose reduction or dose interruption in any of the patients.

Cardiac valvular abnormalities (dabrafenib or dabrafenib-trametinib)*:* Data from preclinical studies suggested that dabrafenib has the potential to cause cardiac valve abnormalities. In a 28-day dog toxicology study, high doses (50 mg/kg/day; approximately 40-fold over the therapeutic dose) of dabrafenib in 1 dog (n=10) resulted in hypertrophy of the right atrio-ventricular valve (tricuspid valve). Therefore, this was monitored in clinical trials with echocardiograms.

Cardiomyopathy (dabrafenib-trametinib**):** Cardiomyopathy has been associated with trametinib use and therefore the incidence was increased in the dabrafenib-trametinib combination compared to dabrafenib alone. Cardiac-related AEs occurred in 9% of subjects in the Part C 150/2 group, which is the same incidence as in the Trametinib ISS population (9%), but a higher incidence compared with the Dabrafenib ISS population (2%) (IB, 2013). Decreased ejection fraction was the only AE reported in the Part C 150/2 group, and all reports were either grade 1 or 2.

Ocular adverse events: Ocular events occurred at a higher frequency in study BRF113220 Part C 150/2 combination group (25%) compared to trametinib (13%) and dabrafenib (8%) monotherapy ISS populations (IB, 2013). Blurred vision, dry eye, and visual impairment were the most commonly reported ocular events in the Part C 150/2 group. All ocular events in Part C 150/2 were grade 1 to 2 with the exception of one case of grade 3 retinal pigment epithelial detachment (RPED).

RPED and RVO *(dabrafenib-trametinib):* These two events are associated with trametinib therapy and therefore were observed in the combination of dabrafenib and trametinib. Of 365 subjects in Study BRF113220, the incidence of RPED remained at 1% and is thus similar to the frequency observed in the overall trametinib development program so far. Thus, the addition of dabrafenib appears to have no impact on the frequency or severity of RPED previously reported for trametinib.

RVO has not been reported as an AE in the dabrafenib ISS population of 586 subjects. Addition of dabrafenib to trametinib in the combination treatment regimen in Study BRF113220 did not increase the frequency of RVO observed thus far with trametinib monotherapy.

Uveitis, iritis, and iridocyclitis (dabrafenib or dabrafenib-trametinib): Uveitis and iritis can occur when dabrafenib is administered as a single agent or in combination with trametinib. In the 365 subjects with melanoma treated on the dabrafenib-trametinib combination arm in Study BRF113220, the incidence of ocular events including uveitis, iritis, or iridocyclitis was 2%, and responded to symptomatic

therapy, which included primarily the use of topical corticosteroids. This rate is slightly higher than in the dabrafenib ISS population (1%). In addition, the severity of the inflammatory ocular events also appeared to be slightly increased, with 2 cases of uveitis Grade 3 and 1 case of Grade 4.

Hyperglycemia (dabrafenib or dabrafenib-trametinib): Hyperglycemia can occur when dabrafenib is used as a monotherapy or in combination with trametinib. In study BRF112680 (dabrafenib monotherapy), 5/12 patients with a history of diabetes required more intensive hypoglycemic therapy while taking dabrafenib; the incidence of grade 3 hyperglycemia was 6% (12/187) in patients treated with dabrafenib compared with none of the dacarbazine-treated patients. In study BRF113220 (combination with trametinib), the incidence of hyperglycemia was 5% (3/55) in patients treated with dabrafenib-trametinib compared with 2% (1/53) in patients treated with dabrafenib (FDA label).

Pancreatitis (dabrafenib or dabrafenib-trametinib): Pancreatitis (<1%) and/or increased lipase/amylase (2%) have been reported at low frequency with dabrafenib. In the phase 2 combination study BRAF113229, AEs of acute pancreatitis or pancreatitis occurred in six (1%) subjects on the dabrafenib-trametinib arm (IB, 2013), and none with dabrafenib monotherapy. The time to onset of pancreatitis ranged from Study Day 21 to 292 (median: 138 days). At the data cut-off, 4 subjects had recovered from the event of pancreatitis. Discontinuation of study drugs due to pancreatitis was not deemed necessary by the investigators in any of the 6 cases. The incidence of pancreatitis was <1% in the dabrafenib ISS population (2 subjects) and in the trametinib ISS population (1 subject).

Hepatic events (dabrafenib-trametinib combination): In the Part C 150/2 group, 15% of subjects experienced hepatic AEs as compared to 13% of subjects in the trametinib ISS population and 6% of subjects in the dabrafenib ISS population (IB, 2013). Of the hepatic AEs, increased ALT and AST were the most common events in all groups, and most were either grade 1 or 2. No cases of Hy's law were observed among any of the subjects in the BRF113220 study.

Diarrhea (dabrafenib-trametinib combination): The proportion of subjects in the Part C 150/2 group who experienced diarrhea was 36% compared with 49% in the trametinib ISS population and 16% in the dabrafenib ISS population (IB, 2013). Most subjects across the monotherapy and combination therapy dabrafenib and trametinib clinical programs reported grade 1 or grade 2 diarrhea.

Pneumonitis (dabrafenib-trametinib combination): Pneumonitis was not reported as an AE in the 365 subjects enrolled in Study BRF113220 (Investigators Brochure, 2013). However, pneumonitis was the most common drug-related SAE (1% of

subjects) Trametinib ISS population. Overall, the addition of dabrafenib to trametinib does not appear to increase the frequency or severity of pneumonitis previously observed with trametinib monotherapy.

Hypersensitivity: There has been a single report of hypersensitivity (blisters) to dabrafenib, occurring on the same day as the 1st dose of study drug as well as upon rechallenge (IB, 2013). The subject recovered after interruption and then discontinuation of dabrafenib. Grade 1 AEs of blisters on limbs (4 subjects) and drug hypersensitivity (rash, 1 subject) have been reported in previous studies with dabrafenib. However, the precise etiology of these events is unclear.

Hypersensitivity to trametinib was reported by one subject 7 days after starting trametinib who experienced fever, asthenia, visual disturbance, and symptoms suggestive of a hypersensitivity reaction described by the investigator as "vascularity." This subject also developed LFT elevations, lower limb nodules that by biopsy showed "dermo-hypodermatitis with plasmocyte and lymphocyte infiltrate." The subject recovered after discontinuation of trametinib.

Hemorrhages (dabrafenib-trametinib combination): Hemorrahge is an AE identified with the dabrafenib-trametinib combination therapy. Hemorrhages, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with dabrafenib plus trametinib combination therapy (FDA label). In study BRF113220, treatment with dabrafenib in combination with trametinib resulted in an increased incidence and severity of any hemorrhagic event: 16% (9/55) of patients treated with trametinib in combination with dabrafenib compared with 2% (1/53) of patients treated with dabrafenib as a single agent. The major hemorrhagic events of intracranial or gastric hemorrhage occurred in 5% (3/55) of patients treated with trametinib in combination with dabrafenib compared with none of the 53 patients treated with dabrafenib as a single agent. Intracranial hemorrhage was fatal in two (4%) patients receiving the combination of trametinib and dabrafenib.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency (dabrafenib or dabrafenib-trametinib combination): Dabrafenib, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with G6PD deficiency; these patients should be closely observed for signs of hemolytic anemia.

Embryofetal toxicity: Based on the mechanisms of action, dabrafenib and/or trametinib can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses three times greater than the human exposure at the recommended clinical dose. Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended clinical dose.

5.6.2 Additional information for trametinib.

5.6.2.1 Clinical pharmacology of trametinib:

Trametinib is absorbed rapidly with median T_{max} generally occurring 1.50 hours after single oral administration of trametinib under fasting conditions. The absolute oral bioavailability of a single trametinib 2 mg tablet is moderate to high (72%) relative to a co-administered IV microdose.

Following repeat-dosing the mean area under the curve (AUC0-τ) and maximum concentrations (Cmax) increased in an approximately dose proportional manner. Trametinib accumulates with repeat dosing with a mean accumulation ratio at the recommended dose of 2 mg once daily of 5.97 and a terminal half-life of 5.3 days. Steady state is achieved by Day 15.

Trametinib has a high volume of distribution (Vd) of 1060 L. Fecal excretion is the major route of elimination after [^{14}C] trametinib oral dose, accounting for >80% of excreted radioactivity recovered (or 39.2 and 35.0% of the radioactive dose in 2 subjects) while urinary excretion accounted for <19% of excreted radioactivity recovered (<10% of the radioactive dose).

In vitro and *in vivo* data suggest that trametinib is unlikely to affect the PK of other drugs and that the PK of trametinib12 is unlikely to be affected by other drugs. Trametinib is metabolized predominantly via deacetylation which is likely mediated by hydrolytic esterases which are not generally associated with drug interaction risk, nor is it a substrate of P-gp or BCRP.

5.6.3- Other Agent(s):

N/A, no other agents will be used in this trial.

5.7 - Specific results that will be given to participants or their health care providers.

Medically relevant results will be transmitted to patients or the legal guardian, not to the patient's minor son or daughter. Incidental results will be given only if medically critical, i.e., severe, urgent, or actionable. Research results will not be revealed to patients unless there are medically important implications for the patient or the patient's family members. Participants are encouraged to remain in contact with the principal investigator regarding advances in the field, and will be invited to enroll in pertinent future studies. Results from routine and diagnostic studies will be given to participants prior to their discharge from the NIHCC. These results will be discussed in wrap up sessions at the end of the visit or earlier if medical action is required for any given result. Participant's healthcare providers will obtain a copy of these routine tests and procedures upon participant's request.

5.8 Describe questionnaires or other psychological instruments and estimate how long they will take to complete, and whether they address sensitive topics.

Questionnaires and other psychological tools are described on section 5.1.2 and are attached separately.

5.9 Genetic counseling.

Genetic counseling will be performed in person by the principal investigator Dr Juvianee I. Estrada-Veras or by Kevin J. O'Brien NP during the inpatient or outpatient evaluations.

5.10 Description of criteria for withdrawal from study.

For description of criteria for withdrawal from the study, please see descriptions on Section 4.4.

6.0 Description of study population

6.1 Estimated number of participants, enrollment ceiling, and anticipated enrollment by year.

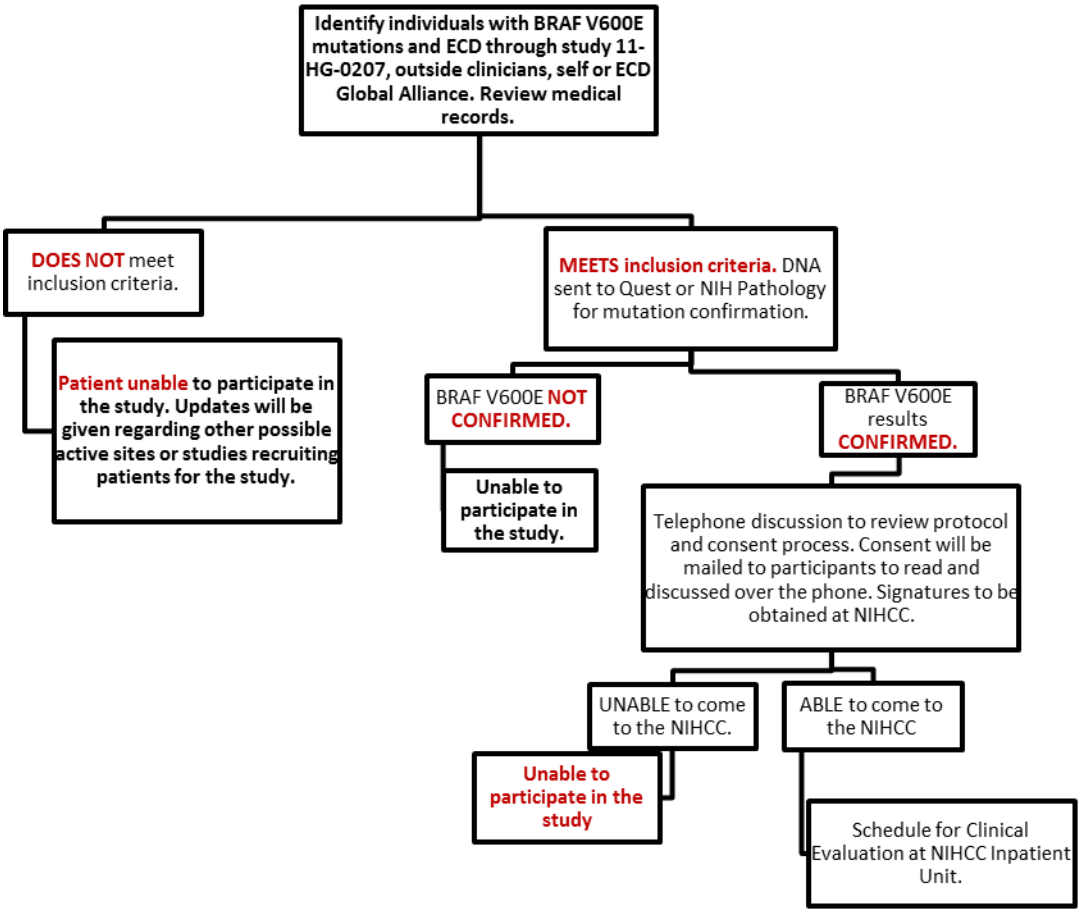
Eighteen patients with a monthly enrollment of 1 or 2. Patients from both genders will be enrolled as well as from any ethnic background.

Table 15. Accrual Targets.

Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	1	+	2	=	3
Not Hispanic or Latino	6	+	9	=	15
Ethnic Category: Total of all subjects	7 (A1)	+	11 (B1)	=	18 (C1)
Racial Category					
American Indian or Alaskan Native	1	+	1	=	2
Asian	1	+	1	=	2
Black or African American	1	+	1	=	2

Native Hawaiian or other Pacific Islander	1	+	1	=	2
White	3	+	7	=	10
Racial Category: Total of all subjects	7 (A2)	+	11 (B2)	=	18 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

6.2 Description and justification of clinical inclusion/exclusion criteria.



6.2.1- Eligibility Criteria

See Figure 1 above for a flowchart regarding eligibility and enrollment procedures.

All patients will be previously or simultaneously enrolled in the natural history ECD protocol #11-HG-0207, "Clinical and Basic Investigations into Erdheim-Chester Disease". Eligible patients must have been diagnosed with Erdheim Chester disease, confirmed by pathological evaluation of the affected tissue with adequate staining. Affected tissue must harbor the BRAF V600E or V600K mutation. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

- Patients must have BRAFV600E or BRAFV600K mutations, identified by an FDA-approved test at a CLIA-certified lab. If test at CLIA-certified lab used a non-FDA approved method, information about the assay must be provided. (FDA approved tests for BRAF V600 mutations in melanoma include: THxID BRAF Detection Kit and Cobas 4800 BRAF V600 Mutation Test).
- Prior treatment, involving interferon, anakinra, imatinib, steroids, chemotherapy with, but not limited to cladribine, vinblastine, 6-mercaptopurine and etoposide, or other medications used empirically for the treatment of ECD, will be acceptable. These therapies should have been completed and discontinued 4 weeks or more prior to enrollment in this study.
- Age ≥18 years. Because no dosing or adverse event data are currently available on the use of dabrafenib in combination with trametinib in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 (Karnofsky ≥70%, see Appendix A). Exception will be made for patients with ECOG performance status ≤ 3 and Karnosfky performance scale ≥ 50%, who require the use of wheelchairs, walkers or canes as well as assistance with daily routines secondary to disabilities caused by ECD cerebellar or brain disease that has been stable for ≥ 3 months.
- Life expectancy of greater than 3 months.
- Able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
- Patients must have normal organ and marrow function as defined below:
  - Absolute neutrophil count (ANC) ≥1.2x10^9/L
  - Hemoglobin ≥9 g/dL
  - Platelets ≥100x10^9/L
  - Albumin ≥2.5 g/dL
  - Serum bilirubin ≤1.5x institutional upper limit of normal (ULN) except subjects with known Gilbert's syndrome
  - Aspartate aminostransferase (AST) and alanine aminotransferase (ALT) ≤2.5x institutional ULN
  - Serum creatinine ≤1.5 mg/dL *OR* calculated creatinine clearance (Cockroft-Gault formula) ≥50 mL/min
  - Prothrombin time (PT)/International normalized ratio (INR) and partial thromboplastin time (PTT) ≤1.3x institutional ULN; subjects receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to randomization.

  - Left ventricular ejection fraction ≥ institutional lower limit of normal (LLN) by ECHO
- Women of childbearing potential must have a negative serum pregnancy test within 14 days of the first dose of study treatment.
- Pregnancy and breast feeding: The effects of dabrafenib and trametinib on the developing human fetus are unknown. For this reason women of child-bearing potential must agree to use adequate contraception (barrier method of birth control, or abstinence; hormonal contraception is not allowed due to drug-drug interactions which can render hormonal contraceptives ineffective) for the duration of study participation, and for at least 2 weeks after treatment with dabrafenib or for 4 months after dabrafenib in combination with trametinib. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

Based on studies in animals, it is also known that dabrafenib may cause damage to the tissue that makes sperm. This may cause sperm to be abnormal in shape and size and could lead to infertility, which may be irreversible.

Safety and efficacy of the combination of dabrafenib and trametinib in pediatric populations have not been investigated. Dabrafenib or trametinib-dabrafenib combination should not be administered to pediatric populations outside clinical trials.

- Based on studies in animals, it is known that dabrafenib may cause damage to the tissue that makes sperm. This may cause sperm to be abnormal in shape and size and could lead to infertility, which may be irreversible. Therefore, male patients should avoid impregnating their partners for the duration of treatment.

- Safety and efficacy of the combination of dabrafenib and trametinib in the pediatric populations have not been investigated. Trametinib and dabrafenib should not be administered to pediatric populations outside clinical trials.
- Therapeutic level dosing of warfarin can be used with close monitoring of PT/INR by the site. Exposure may be decreased due to enzyme induction when on treatment, thus warfarin dosing may need to be adjusted based upon PT/INR. Consequently, when discontinuing dabrafenib, warfarin exposure may be increased and thus close monitoring via PT/INR and warfarin dose adjustments must be made as clinically appropriate. Prophylactic low dose warfarin may be given to maintain central catheter patency.
- Ability to understand and willingness to sign a written informed consent document.

6.2.2 - Exclusion Criteria

- Inability to provide informed consent.
- Prior systemic anti-cancer therapy (chemotherapy with delayed toxicity, extensive radiation therapy, immunotherapy, biologic therapy, or vaccine therapy) within the last

3 weeks; chemotherapy regimens without delayed toxicity within the last 2 weeks preceding the first dose of study treatment.

- Use of other investigational drugs within 28 days (or five half-lives, whichever is shorter; with a minimum of 14 days from the last dose) preceding the first dose of study treatment and during the study. Patients that have used other BRAF or MEK inhibitor are excluded.
- Current use of a prohibited medication. Patients receiving any medications or substances that are strong inhibitors or inducers of CYP3A or CYP2C8 are ineligible. Current use of, or intended ongoing treatment with: herbal remedies (e.g., St. John's wort), or strong inhibitors or inducers of P-glycoprotein (Pgp) or breast cancer resistance protein 1 (Bcrp1) should also be excluded. Below are a few examples of the agents.

Table 16. Prohibited Drugs

PROHIBITED – strong inducers of CYP3A or CYP2C8, since concentrations of dabrafenib may be decreased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Rifamycin class agents (e.g., rifampin, rifabutin, rifapentine),
Anticonvulsant	Carbamazepine, oxcarbazepine phenobarbital, phenytoin, s-mephenytoin
Miscellaneous	bosentan, St. John's wort
PROHIBITED – Strong inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Clarithromycin, telithromycin, troleandomycin
Antidepressant	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Hyperlipidemia	Gemfibrozil
Antiretroviral	ritonavir, saquinavir, atazanavir
Miscellaneous	Conivaptan

Strong inducers/inhibitors of CYP3A, CYP2C8, Pgp, and Bcrp are prohibited since they can affect the concentrations of dabrafenib.

The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on study treatment. (Megestrol [Megace], if used as an appetite stimulant, is allowed.)
- Concurrent treatment with bisphosphonates is permitted; however, treatment must be initiated prior to the first dose of study therapy. Prophylactic use of bisphosphonates

in patients without bone disease is not permitted, except for the treatment of osteoporosis.

- Because the composition, PK, and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is prohibited during the study (including, but not limited to, St. John's wort, kava, ephedra [ma huang], ginkgo biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, or ginseng).

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/main-table/; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Appendix C is a patient information sheet that can be used for this specific protocol and presented to the patient.

-Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0) grade 2 or higher from previous anti-cancer therapy, except alopecia.

-Human Immunodeficiency Virus (HIV)-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with dabrafenib.

- A history of Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection (with the exception of cleared HBV and HCV infection, which will be allowed).

- Presence of malignancy other than the study indication under this trial within 3 years of study enrollment.

- Patients with history of RAS mutation-positive tumors are not eligible regardless of interval from the current study. Note: RAS testing and absence of RAS mutation are required for eligibility.

- Leptomeningeal or brain metastases or metastases causing spinal cord compression that are symptomatic or untreated or not stable for ≥3 months (must be documented by imaging) or requiring corticosteroids. Subjects on a stable dose of corticosteroids >1 month or who have been off of corticosteroids for at least 2 weeks can be enrolled with approval of the CTEP medical monitor. Subjects must also be off of enzyme-inducing anticonvulsants for >4 weeks.

- History or evidence of cardiovascular risk including any of the following:

- QT interval corrected for heart rate using the Bazett's formula QTcB ≥480

msec.

- History of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within the past 24 weeks prior to randomization.
- History or evidence of current Class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
- Intra-cardiac defibrillators.
- Abnormal cardiac valve morphology (≥ grade 2) documented by ECHO; (subjects with grade 1 abnormalities [*i.e.*, mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.
- History or evidence of current clinically significant uncontrolled cardiac arrhythmias; clarification: Subjects with atrial fibrillation controlled for >30 days prior to dosing are eligible.
- Treatment refractory hypertension defined as a blood pressure of systolic >140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy

- History of interstitial lung disease or pneumonitis not due to ECD.
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO).
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, diabetes mellitus, hypertension, or psychiatric illness/social situations that would limit compliance with study requirements.
- History or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) including presence of predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes); or visible pathology (e.g., evidence of optic disc cupping, evidence of new visual field defects on automated perimetry, or intraocular pressure >21 mmHg as measured by tonography) as assessed by ophthalmic examination.
- Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with dabrafenib, breastfeeding should be discontinued if the mother is treated with dabrafenib. These potential risks may also apply to other agents used in this study.
- Inability to travel to the NIH Clinical Center.
- Patients with wild type BRAF gene molecular results on Erdheim Chester disease affected tissue.
- Patients with confirmed diagnosis of ECD that are asymptomatic and with no visceral involvement are not eligible for this trial (Patients with no target lesions as per RECIST 1.1 criteria.

6.2.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

6.3 Location of study

Patient will be seen and evaluated at the NIH Clinical Center inpatient unit or outpatient clinic according to the study calendar.

6.4 Description of recruitment strategies

Most often, patients call the Principal Investigator at the suggestion of the ECD Global Alliance, a family-patient organization that has its own web site and contact information. In addition, the medical community knows of the Principal Investigator's interest in ECD, and refers patients. Patients with the pathologic findings of ECD and BRAFV600E mutation are immediately accepted for possible enrollment. See figure 1 on section 6.2.1 for a flowchart explaining the recruitment strategies.

6.5 For existing sample/data sets, note whether samples were originally collected for research or clinical practice. If obtained for research, include a description of the original purpose of study and prior plans for sample storage. Was consent obtained that would be applicable to this study?

Patients enrolled on NHGRI Protocol 11-HG-0207 are potential candidates for this trial as long as the BRAF mutations V600E or V600K were detected in their samples. These samples were collected for clinical diagnostic as well as research purposes and consent was obtained at moment of enrollment to the natural history study. The clinical use of these samples was to confirm the pathological diagnosis of ECD. These samples were then analyzed under research for BRAF mutation testing which was then CLIA certified. Patients that will be considered as enrollees to this trial, but are unknown to our natural history study, will be enrolled on study 11-HG-0207 and tissue will be collected for confirmation of BRAF status prior to enrollment into this clinical trial. The 11-HG-0207 patient subject consent form is attached as Appendix 3.

6.6 Description of any financial compensation. If participant withdraws early, describe whether compensation will be modified.

NA.

7.0 Description of study statistical considerations and/or analytic plan:

7.1- STATISTICAL CONSIDERATIONS

7.1.1- Study Design/Endpoints

Patients with BRAFV600E positive Erdheim Chester disease will be enrolled in this study and will be evaluated at the NIH Clinical Center in Bethesda, Maryland. Patients will be referred to this trial from NHGRI protocol 11-HG-0207, which performs clinical and basic investigations into Erdheim Chester disease. Referrals will also be accepted from treating physicians, the ECD Global Alliance and patients themselves. Patient will be admitted for 4-5 days at the NIH Clinical Center and baseline testing will be performed prior to the first dose administration. Patients without progression or significant AEs may continue therapy for a maximum of 12 months. At six months, patients without RECIST- defined response or major clinical improvement may elect to discontinue therapy. There will be no randomization due to the rarity of the disease and small patient population. Patients will be seen once at the start of their participation in the trial, and again 1 week, 1 month, 2 months, 4 months, and 6 months, 8 months, 10 months and 12 months after the initial admission. At 12 months, therapy will be stopped and follow up will be for one year after completion of therapy at 15 months, 18 months and 24 months, but for proper analysis of treatment response and other variants, follow up could be prolonged. It is our intention to recruit at least 18 patients within approximately one year. In addition, we have access to approximately 100 cases in the USA and worldwide through the ECD Global Alliance. No placebo will be used and patients must stop their current ECD treatment at least 4 weeks before enrollment; this applies to cases in which the patient is not responding to current treatment.

To determine the clinical response rate, baseline measurable disease, as per RECIST 1.1 criteria, will be determined less than 4 weeks prior to the start of treatment or at the baseline visit. Patients with ECD must have measurable or evaluable disease in one or more systems. These can include, but are not limited to, the retro-orbital space, pituitary stalk, cerebellum, brainstem, heart, retroperitoneal space causing renal and aortic encasement and long bones of upper and lower extremities. Complete response can be determined through imaging studies of these areas. As described in the treatment plan, imaging studies will be performed including retro-orbital/pituitary/brain/cerebellar MRI, abdomen and pelvis CT, and cardiac CT and MRI. FDG PET scan and T-99m bone scan will also be performed as exploratory outcome measures. The required imaging study will be selected on a case-by-case basis since the disease is heterogeneous in its presentation. Response to therapy will be evident on follow up imaging studies revealing a decrease in lesion size of 30% or more, which is defined as a partial response as per RECIST Criteria, when compared to baseline studies. After 12 months of therapy have been completed, patients will go to an off therapy follow up period that will have follow up visits at 15 months, 18 months and 24 months. During this period, duration of response will be assessed through

imaging studies of the patient's target lesions. If these target lesions show an increase, in at least one diameter, of 20% or more when compared to that target lesion measurement when they completed 12 months of therapy, this will be considered recurrence/progession of disease. Patients with disease recurrence will be considered for therapy resumption at the dose they were on when they completed therapy. Patients considered for therapy resumption will need to meet all inclusion and exclusion criteria and have new registration and TAC. They will also follow the safety guidelines for toxicity and dose modifications.

Besides imaging follow up, duration of response will be also assessed through patient's report of symptoms according to the MD Anderson symptom inventory, quality of life measures and SUV values on PET scan. Cytokines will also be followed during this period. All these parameters will help us determine disease recurrence-progression on each case.

The study will be conducted as an optimal Simon two-stage phase II trial in order to rule out an unacceptably low 10% clinical response rate (PR+CR: p0=0.10) in favor of a targeted rate consistent with 40% (p1=0.40). Maximum trial size would be set at 18 evaluable patients. If at least 4 responses (at least 22%) were observed among the 18 evaluable patients, this regimen would be considered worthy of further testing in this disease. If no responses were observed among the initial 6 patients, the study would be terminated early and declared negative. This design yields at least 90% power to detect a true response rate of at least 40%. It yields at least .90 probability of a negative result if the true response rate is no more than 10%, with at least .59 probability of early negative stopping. A temporary pause in the accrual to the trial may be necessary to ensure that enrollment to the second stage is warranted.

To ensure safety and feasibility of the selected dose for patients with ECD, we will assess the toxicity profile and dose delivery after the first 6 subjects have completed 3 months of therapy. If 3 or more individuals do not take at least 80% of the full doses of both drugs over 3 months due to dose modification for toxicity, revision of the dose schedule should be considered. Safety will be monitored on a continuous basis and feasibility of drug administration will be reviewed after 12 patients and then 18 patients have completed the 3 months of therapy.

All patients who receive any amount of the study drug will be evaluable for toxicity. Toxicity and doses adjustment will be perform as per the guidelines discussed on sessions 4.7 and 9 where dosing modifications and adverse events are discussed. Reassessment of the dose-schedule when 3 months or 12 cycles of therapy are completed will be performed by collecting the patient's medication diary information. This information will be collected by the study PI or the study coordinator by direct communication with the patient.

Besides response measured through imaging studies, physical and emotional well-being will be evaluated to assess improvement in daily living as exploratory endpoints. These

evaluations will be performed by the rehabilitation medicine and pain and palliative care teams during the treatment part of this trial as well as the off therapy follow up period. The list of tools and evaluations is available on sections 4.1.2 and 11.3.

7.1.2- Stratification Factors

N/A

7.1.3- Analysis of Secondary Endpoints

As secondary evaluations, time to response, duration of response, PFS and OS will be reported separately using Kaplan-Meier curves and appropriate 95% confidence intervals. Every report will contain all patients included in the study. These findings will be compared informally to other similar published results in patients with the same disease.

Other exploratory analyses will include FDG-PET, CT, bone scans, and levels of C-reactive protein, ESR, and cytokines. There are no specific ECD biomarkers that can be measured in blood, urine or tissue in order to assess disease activity.

In patients affected by central nervous system disease (mainly cerebellar and brain stem disease), improvement in overall physical function and conditioning will be assessed. Patients will be evaluated by rehabilitation medicine and neurology. Improvement of their overall quality of life will be evidence of response, and assessments will be made at baseline and throughout the trial, as well as at the conclusion of the trial, to evaluate for any improvement in quality of life.

Resistance to therapy will be evaluated through imaging studies and patient follow up for at least one year, but this is not expected with the combination therapy.

7.1.4- Reporting and Exclusions

<u>Evaluation of Toxicity</u>

All patients will be evaluable for toxicity from the time of their first treatment with Dabrafenib mesylate (GSK2118436B, NSC 763760) and Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093).

CTEP is the sponsor of the trial. The principial investigator and study data manager will monitor the safety data. CTEP will be notified of serious adverse events as soon as the PI, associate investigator or study data manager are aware of them through the expedited reporting systems and all AEs through the routine reporting to CDS. The National Human Genome Research Institute Intramural Data Safety and Monitoring Board (DSMB) will also monitor this trial. Monitoring by the DSMB will include receipt of quarterly updates regarding the trial status and accrual with a report every 6 months summarizing safety data as provided by the investigational staff. The DSMB will follow the protocols stopping

guidelines for serious adverse event as described in sections 4.7 and 9. Timing of the reports may be adjusted based on the rate of enrollment or any other circumstance that might warrant increased monitoring, for example if more than expected adverse events are reported on the quarterly updates, safety data reports may be available sooner than 6 months.

The NHGRI DSMB is led by Pamela West, executive secretary, NHGRI DSMB. Other DSMB members include physicians and ethicists. Three members of the DSMB are from outside NIH and one is from within the NIH.

Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All the patients who met the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 4-9 will be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions will be based on all eligible patients. Subanalyses will be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported. The 95% confidence intervals will also be provided.

8.0 Description of potential benefits of study:

8.1 Direct benefits to participants

This study has only a small chance of a direct benefit for the participant because we do not know if the study drug/study approach is effective. This study may help researchers learn things that may help other people in the future.

8.2 Collateral benefit to participants

Individual patients will have the benefit of improved accuracy of diagnosis and prognosis due to greater experience and knowledge by a physician caring for a large number of ECD patients. The results of testing performed at the Clinical Center will provide baseline or follow up medical data for each patient. The Principal Investigator serves as a resource for consultation with referring physicians.

8.3 Benefits to society

This protocol should elucidate the clinical breadth of ECD, and provide new approach to treatment of this rare disorder

9.0 Description of likelihood and seriousness of harms and how safety will be maximized:

9.1 Therapeutic Interventions – Adverse Events: List and Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 9.1.1) and the characteristics of an observed AE (Section 9.1.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

9.1.1- Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

CAEPRs for CTEP IND Agent(s)

CAEPR for Dabrafenib and Trametinib.

9.1.1.1- Comprehensive Adverse Events and Potential Risks list (CAEPR) for Dabrafenib mesylate (GSK2118436B, NSC 763760) and Trametinib dimethyl sulfoxide (GSK1120212B, NSC 763093)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list

of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 691 patients for Dabrafenib Mesylate and 968 for Trametinib dimethyl sulfoxide* . CAEPR for Dabrafenib mesylate (GSK2118436B) and Trametinib dimethyl sulfoxide (GSK1120212B) are available on Appendix 2.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

9.1.2- Adverse Event List(s) for *[Other Investigational Agent(s)]*

N/A

9.1.2.1- Adverse Event List(s) for Commercial Agent(s)

N/A

9.1.2.2- CAEPR for [CIP IND Agent #1)]

N/A

9.1.2.3- Adverse Event List(s) for CIP (*e.g.* Study-Specific) Commercial Imaging Agents

N/A

9.1.3- Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

For expedited reporting purposes only:

- AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 9.1.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
- Other AEs for the protocol that do not require expedited reporting are outlined in section 9.1.1.1 and 9.1.4

- **Attribution** of the AE:
  Definite – The AE *is clearly related* to the study treatment.
  Probable – The AE *is likely related* to the study treatment.
  Possible – The AE *may be related* to the study treatment.
  Unlikely – The AE *is doubtfully related* to the study treatment.
  Unrelated – The AE *is clearly NOT related* to the study treatment.

9.1.4- Expedited Adverse Event Reporting

Expedited AE reporting for this study must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 9.1.4.1).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

9.1.4.1- Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Table 17. Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization
≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization
≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

Not Applicable.

9.1.5- Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

9.1.6- Secondary Malignancy Due to Prior Treatment or Interventional Therapy

In these cases, a *secondary malignancy* is a cancer caused by treatment for a previous

malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). In these cases, a secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

9.1.7- Second Malignancy Unrelated to Prior Treatment or Interventional Therapy

In these cases, a second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). CTEP requires all second malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS.

9.2 Diagnostic interventions

Risks from diagnostic interventions are minimal. A physical risk of this study consists of the phlebotomy requirement. Blood drawing can cause a small amount of discomfort and possible bruising or redness from a small needle puncture. Rarely, some people faint from blood drawing.

Electrocardiogram and echocardiogram do not involve radiation and are minimal risk. However, these studies may be uncomfortable for the patient, due to the use of probes and instruments placed on the patient's skin. In the heart tracing, electric signals produced by the heart are measured by probes that are placed on the skin surface. There are times when shaving of chest hair is needed for this test. The echocardiogram uses soundwaves to show pictures of the heart using an instrument called a transducer placed on the skin of the patient's chest.

Discomforts also include the venipunctures themselves (usually 2 per admission) and 24-hour urine collections

9.3 Radiation

The imaging studies proposed for staging and follow up of target lesions in this trial are all clinically indicated in the diagnosis of Erdheim Chester disease and are also indicated for the proper follow up of patients undergoing active therapy.

For cancer, it is necessary to do the imaging for proper evaluation of treatment efficacy and since these treatments are also toxic, serial radiological assessments are needed in order to discontinue treatments that are ineffective. CT scan as well as PET/CT scan and other nuclear medicine studies are common clinical practice in cancer care. ECD is not yet considered a malignancy, but emerging research indicates that besides BRAF, other RAS genes are involved and some researchers postulate oncogene-induced senescence as a possible pathophysiological mechanism making this disease to behave as a low grade malignancy. Having multiple tests using radiation, increases the possibility of cancer induction due to radiation exposure; this will be discussed at the time of recruitment.

9.4 Sedation

The use of sedation will be primarily for clinical purposes. However, there may be circumstances where sedation is required for procedures that are strictly for research. For example, procedures such as the tissue biopsy (including, but not limited to, bone marrow, core bone, and perirenal biopsy) or imaging studies will require sedation. The tissue biopsies will be clinically indicated procedures (e.g., tissue collection for mutant BRAF status) and research procedures (e.g., tissue collection for proteomic analysis). It is our intention to use sedation primarily when clinically indicated, but there may be times when the use of sedation for tissue collection will be needed for the purpose of research, (e.g., tissue collection to evaluate regression of hisiocytic infiltration and proteomic analysis). This will help the participant tolerate the procedure with minimal or no discomfort. The risks associated with this include, but are not limited to, allergic reaction to the sedative used, amnesia, airway obstruction, apnea, hypotension and hallucinations. Healthcare professionals trained to respond to these events, as well as the necessary medical equipment, will be available at the bedside. This will be discussed with the participant prior to consent signature.

9.5 Psychological harms

The main psychological issues will be the acquisition by the patient of a new awareness concerning ECD and new hope for a cure. Learning the likelihood of other complications is usually part of the motivation behind a patient's enrolling in this protocol. Lack of therapeutic efficacy will be a challenging situation for the patient. Facing this reality can be besides challenging, depressing, so counseling will be available. Incomplete understanding is always a risk, but should be minimized by the availability of counseling and consultation through the principal investigator.

Also, some people have had problems getting jobs or life insurance policies as a result of participating in genetic studies. These situations might cause emotional and financial stress. While it is our policy to protect privacy and confidentiality and not to disclose genetic information, we cannot guarantee complete confidentiality. There may be rare instances when we are required by law to release information without permission. If such an instance occurs, we will attempt to notify the patient.

9.6 Risks to family relationships.

This protocol may reveal unexpected family relationships such as adoption or misattributed parentage, but if these issues do arise, we will not mention them to the patient or family members, unless medically or genetically significant information is found. Every attempt will be made to uphold the objective of privacy and subject autonomy.

9.7 Discrimination.

Patients enrolled in this protocol already have ECD. However, the hematologic and pulmonary complications among others may create additional issues vis-à-vis insurability and employment. To the fullest extent possible, the investigators will not disclose to third parties any information about the participants without their expressed consent. The risks of genetic (DNA) testing include concern over the specific DNA results found and failure to keep the genetic information private. However, medical data collected for this protocol will be treated confidentially, as is standard for patient-related information.

10 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

10.1 Will participant identifiers be attached to data, or will samples/data be coded or unlinked?

Patient samples will be coded on arrival. However, the identifier will be attached to the data, all of which will be maintained in records in a locked file cabinet and a research database such as Lab Matrix within a secured laboratory on the NIH main campus in Bethesda, MD. Besides LabMatrix and after the approval of amendment E, the research team will be using the NICHD electronic data capture system, the Clinical Trials Database (CTDB) as a complimentary data base. Data entered directly in CTDB will be considered digital source documentation. The Clinical Trials Database Project (CTDB) assists Investigators with the management of natural history and clinical trial research projects. Associated with the project are two major components: (1) a set of information technology systems based upon

industry standard technologies and best practices (e.g. Java, XML, UML); and (2) a team of support staff that assist investigators with designing and executing research projects. CTDB is 21 CFR Part 11 Compliance certified. The CTDB is a web-based application that supports flexible data capture, and reporting. The system is hosted at the NIH in Bethesda, MD and was pushed to production in 2004. It is accessible via the Internet through the NIH firewall, on both Mac and Windows based computers. An Oracle relational database is utilized to capture and secure data entered through the web interface.

Access to this research databases will be limited to the investigators and laboratory staff involved in this project. Patients' medical summaries and other documents sent to us upon referral to this study will be kept in a locked file cabinet on the NIH campus.

10.2 Description of any clinical/demographic information that will be included.

This will be part of the clinical data kept in a locked file within a secured laboratory on the NIH campus.

10.3 How might this information make specific individuals or families identifiable?

Patients enrolled in this study are from all over the world. It is doubtful that any demographic information could identify an individual. However, if an ECD patient lived in a small town, and information revealed that the person was enrolled in this study, the patient might be identified as having ECD.

10.4 If research data will be coded, how will access to the "key" for the code be limited? Include description of security measures (e.g., *password-protected database, other*). List names or positions of persons with access to the "key" for the code.

The code to patient identities, as well as other patient data, will be kept in a password protected database. Access to the code will be restricted to the principal investigator, Dr. William A. Gahl. This protected database will contain patient's information obtained at the NIH visit. The results of research and relevant tests and procedures done at the NIH will also be kept in this protected database.

10.5 Will pedigrees be published? Include description of measures to minimize the chance of identifying specific families.

Partial pedigrees or pedigrees that are not identifiable may be published. Elements that could uniquely identify a pedigree will be disguised by, for example, not specifying the genders of certain members.

10.6 Will results be provided to participants?

All clinical data will be given directly to the patients at a debriefing session just prior to discharge.

10.7 Will personally identifiable information be released to third parties?

The investigators will not disclose to third parties any information about the participants without their expressed consent, unless required by law.

10.8 Under what circumstances will data/samples be shared with other researchers or deposited in various repositories, biobanks, and/or databases voluntarily or as mandated by NIH policies (e.g. dbGaP)?

Biologicals and data may be shared with collaborators within NIH, but will not be transferred to another site with any identifiers. Patient's biologicals and data can be shared with ECD investigators outside of the NIH, but these samples and data will be de-identified and patients will provide permission to allow for their samples and data to be shared. Also, requests by the patient to transfer samples to another laboratory will be honored if reasonable, e.g., if another investigator offers a diagnostic test not offered by this protocol. Questionable requests will be referred for IRB or ethics review.

10.9 Describe any additional features to protect confidentiality.

No other features will be used to protect confidentiality at the moment

11.0 Assessment of risk/benefit ratio

This is a phase II, interventional study enrolling adults with Erdheim Chester Disease. This study will not enroll children or adults who are or may be unable to provide consent. This study involves greater than minimal risk, but presents the prospect of direct benefit to individual subjects from the intervention being tested. This study also presents the possibility of yielding generalizable knowledge about the disease under study, Erdheim Chester Disease, which could directly or indirectly influence the care of patients with ECD in the future.

12.0 Unanticipated Problems: Collection, monitoring, analysis and reporting of adverse events and protocol deviations

12.1 Exclusion of adverse event reporting for a natural history protocol.

N/A

12.2 Monitoring of adverse events related to this protocol.

Adverse events, protocol deviations, unanticipated problems (UP), Unanticipated Adverse Device Effects (UADEs), serious adverse events, sponsor and serious, are defined as described in NIH HRPP SOP 16 ("Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations"). All adverse events occurring during the study, including those observed by or reported to the research team, will be recorded. Serious unanticipated problems, Unanticipated Adverse Device Effects and serious protocol deviations, will be reported to the IRB and CD (Clinical Director) as soon as possible but not more than 7 days after the PI first learns of the event. Not serious unanticipated problems will be reported to the IRB and CD as soon as possible but not more than 14 days after the PI first learns of the event. Not serious protocol deviations will be reported to the IRB as soon as possible but not more than 14 days after the PI first learns of the event.

Deaths will be reported to the Clinical Director within 7 days after the PI first learns of the event.

12.3 Data Safety and Monitoring Board.

This protocol offers therapeutic interventions and a DSMB is indicated, but CTEP will lead the monitoring of this trial.

13.0 Description of alternatives to participation

We know of no other therapeutic clinical trial studying exclusively the efficacy of targeted therapy on BRAF V600E mutated ECD. Patients are welcome to participate in other research studies in ECD that are available in the USA and Europe. Currently, this is the only study that is treating ECD patients without having patients with other malignancies in the cohort.

14.0 Description of consent process

14.1 Who will obtain consent?

Either the Principal Investigator or an Associate Investigator will obtain consent.

14.2 Setting where consent will be obtained.

Consent will be obtained on the inpatient ward or outpatient clinics of the NIH Clinical Center.

14.3 What information will be provided to participants?

A copy of the consent form will be given to each participant for their records.

14.4 Protections for participants who may be vulnerable to coercion or undue influences.

This study will enroll adults with Erdheim Chester Disease. We will not enroll children, pregnant women, prisoners, healthy volunteers, or adults with impaired decision-making ability. Children are excluded from this study, because no dosing or adverse event data are currently available on the use of dabrafenib in combination with trametinib in patients under 18 years of age. Pregnant women and fetuses are excluded from this study, because BRAF inhibitors, as well as other therapeutic agents used in this trial, are known to be teratogenic (causing physiological abnormalities during development) to fetuses. Prisoners will not be enrolled, because of their inability to comply with the requirement to visit the NIH Clinical Center on a regular basis for study visits. Adults who are or may be unable to provide informed consent and adults with impaired decision-making ability, will not be enrolled to the study, because of their anticipated inability to comply with the complex and rigorous study procedure requirements. If at any time during the study a subject loses the ability to provide informed consent or develops impaired decision-making ability, the subject will be withdrawn from the study.

Potential participants who are also NIH employees will not be excluded based solely upon their affiliation with NIH. However, due to the rare nature of the disease being studied, the disabling course of the disease, and the small number of subjects to be enrolled, it is extremely unlikely that any potential subjects we enroll will also be NIH employees. At this time, we do not anticipate enrolling any NIH employees into this study.

14.5 Are there special circumstances regarding obtaining consent?

We anticipate that all potential participants will be proficient with the English language and will be consented in English. However, we will not exclude potential participants, who are otherwise eligible, based upon their inability to be consented in English. In those cases, we will submit an action to the IRB for the use of the short form and will use an interpreter to conduct the informed consent with one of the study investigators present. We also anticipate that all potential participants will undergo all studies and procedures in order to meet our objectives and successfully conclude our trial.

15.0 Description of any financial compensation

N/A

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